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Endocrine and immune correlates of cognitive impairments, depression, and fatigue in HIV/AIDS.

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NOTE TO USERS

Endocrine and Immune Correlates of Cognitive Impairments, Depression, and Fatigue in HIV/AIDS

by

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Abstract

Objective: This pilot study aimed to advance our current understanding of the role of biological processes in the development of specific neuropsychiatric complications in HIV/AIDS. In particular, this project explored whether elevated systemic indicators of immune system (i.e., IL-6, TNF-alpha, and neopterin) and hypothalamic-pituitary adrenal axis (HPA) activation (i.e., cortisol) were associated with commonly reported clinical symptoms of cognitive impairment, fatigue, and depression.

Method: Thirty-one HAART-naïve adults (i.e., no past or current use of antiretroviral medications) adults with HIV infection completed subjective symptom questionnaires and neuropsychological tests. Blood samples were obtained and processed at three separate laboratories. One-tailed Spearman correlations were used to examine the relations between serum concentrations of immune and HPA factors, cognitive impairments (learning efficiency, attention/working memory, and psychomotor processing speed), and subjective symptoms (fatigue, depression, cognitive complaints, and general illnesses).

Results: Neuropsychological impairment was not associated with the levels of biological markers. Depressive symptoms were, however, modestly associated with elevated IL-6 mRNA expression ($r_s = 0.40$, $p < .05$) even after removing the influences of fatigue, total cognitive complaints, and illness symptoms ($pr = 0.39$, $p < .05$). Elevated serum neopterin was strongly associated with depressive symptoms in individuals taking antidepressants ($r_s = 0.83$, $p < .001$), though the association was nullified in the group not taking any antidepressants ($r_s = -0.25$, $p > .05$). More specifically, mean neopterin levels were higher in the depressed as compared with non-depressed group but only for those individuals taking antidepressants [$F(1, 11) = 45.66$, $p < .001$].

Conclusion: Increased subjective symptoms, especially depression, may be associated with elevated immune activation (i.e., higher levels of IL-6 mRNA and neopterin) in some individuals with HIV infection. While antidepressants may exert immunosuppressive effects in treatment-responsive individuals, treatment-resistant individuals may continue to have both elevated depressive symptoms and neopterin levels despite presumably therapeutic doses of antidepressants. Although replication in a larger sample is needed, these preliminary findings suggest that systemic biological markers (especially neopterin) may be useful in differentiating individuals at greater risk of developing chronic, debilitating depression. Implementation of alternative interventions may be necessary to alleviate depressive symptoms in this selective group and ultimately improve their quality of life.

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CHAPTER I

Introduction

Since the human immunodeficiency virus (HIV) was identified as the causative agent for Acquired Immunodeficiency Syndrome (AIDS) in 1984, extensive research has been aimed at decelerating the worldwide spread of this devastating and life-threatening disease (Gallo et al., 1984). Initial investigations primarily centred around delineating the pathogenesis of HIV in attempt to develop drug therapies that interfere with the viral invasion and replication process. Combination highly active antiretroviral therapy (HAART) agents have proven effective at slowing disease progression (Carpenter et al., 2000; Chaisson, 1998; Sendi, Bucher, Craig, Pfluger, & Battegay, 1999), though considerable variability in the rate of progression and clinical course of HIV infection still exists (Bouwman et al., 1998; Weber, 2001). New issues in clinical management have concurrently emerged with medical advancements and prolonged life expectancy. Individuals with HIV infection frequently report that the presence of cognitive impairments, somatic symptoms (especially chronic fatigue), and/or psychiatric difficulties adversely impacts their activities of daily living and quality of life. The causes and pathological processes underlying these symptoms in HIV/AIDS remains unclear. More multidisciplinary research is needed to identify specific factors (both biological and psychosocial) that explain some of the variability in clinical manifestations and predict at-risk individuals suitable for early interventions aimed at managing clinical symptoms and improving quality of life.

Recent work in the area of psychoneuroimmunology highlights the need to consider the role biological processes play in mediating somatic, cognitive, and psychological symptoms in various illnesses. Although the significance of cytokine and hypothalamic-pituitary-adrenal (HPA) dysregulation in the neuropathogenesis of HIV has been described at a cellular mechanistic level (e.g., Brooke & Sapolsky, 2000; Gendelman, Lipton, Tardieu, Bukrinksy, & Nottet et al., 1994; Goodkin, Baldewicz, Wilkie, Tyll, & Shapshak, 2001; Kumar, Kumar, Waldrop, Antoni, & Eisdorfer, 2003), generalization of these findings to the broader clinical level is not readily apparent. To date, studies have generally focused on determining systemic (e.g., CD4 cell count, viral load, and cytokine) or central nervous system (CNS) (e.g., levels of HIV gp120 viral proteins or neurotoxin production) biological markers of *global* levels of neurological functioning and disease progression in HIV/AIDS (e.g., Brookes & Sapolsky, 2000; Childs et al., 1999; Dal Pan et al., 1998; Griffin, McArthur, & Cornblath, 1991; Ryan et al., 2001). Various psychosocial risk factors have also been related to overall disease progression in HIV and the development of HIV-related medical symptoms, though more research is needed to delineate the immunological and neuroendocrine mechanisms suspected of influencing this relationship (e.g., Balbin, Ironson, & Solomon, 1999; Cole, Kemeny, Fahey, Zack, & Naliboff, 2003; Kemeny, 2003). A paucity of literature still exists on the pathophysiology underlying the manifestation of *specific* neuropsychiatric complications in HIV/AIDS.

This exploratory study was designed to expand upon these previous studies by investigating the potential link between systemic biological markers (i.e., cortisol, IL-6, TNF-alpha, and neopterin) and the presence of *specific* clinical symptoms in adults with

HIV/AIDS: cognitive impairments (i.e., attention and working memory, learning efficiency, and psychomotor/processing speed), fatigue, and depression. In the following sections, current literature providing the rationale for this pilot project will be outlined in more detail. First, the prevalence, functional implications, and potential relations between cognitive, somatic, and depressive symptoms will be reviewed. Next, a brief overview of the physiological and behavioural changes associated with activation of immune-endocrine-neurotransmitter pathways will be provided. The brain-behavioural consequences of dysregulation of this biological pathway documented in previous studies of healthy controls, other medical illnesses, and mood disorders will be described. Then, possible biological mechanisms contributing to brain-behaviour dysfunction in HIV infection will be reviewed at systems, cellular, and molecular levels. Finally, the goals and hypotheses of the present study will be outlined.

Prevalence and functional impact of cognitive symptoms in HIV/AIDS

Self-reports of cognitive symptoms, occurring in about 40 to 50% of adults with HIV infection, commonly include slowed thinking, reduced attention span, increased distractibility, forgetfulness, difficulty at simultaneously completing more than one task, and blocking on words (Gibbs, Andrewes, Szmukler, Mulhall, & Bowden, 1990; Mehta et al., 1996). A similar proportion of individuals demonstrate cognitive impairments on neuropsychological tests, with the prevalence estimated to increase with advancing disease stage from about 30% of asymptomatic individuals to 56% of individuals diagnosed with AIDS (Bornstein et al., 1993; Heaton et al., 1995; White et al., 1995). Cognitive impairments can range from milder difficulties primarily seen in areas of attention and working memory, verbal fluency, learning efficiency, and

psychomotor/processing speed (MCMD: HIV-associated minor cognitive/motor disorder) to profound dementia (HAD: HIV-associated dementia complex) (Janssen et al., 1991). Despite advances in HAART medication, HAD continues to develop in about 15% of individuals with AIDS (McArthur, Sacktor, & Selnes, 1999). HAD resembles a subcortical pattern of dysfunction characterized by slowed cognitive processing, impaired recall of information, problems with attention/concentration, motor disturbances (e.g., slowing, unsteady gait, tremor, and leg weakness) and behavioural changes (e.g., apathy, irritability, loss of libido, and social withdrawal).

These cognitive difficulties can adversely affect everyday functioning to varying degrees. Studies have documented associations between cognitive impairments in individuals with HIV infection and poorer quality of life (Kaplan et al., 1995; Tozzi et al., 2004), higher rates of unemployment and decreased work efficiency for those still employed (Albert et al., 1995; Benedict, Mezhir, Walsh, & Hewitt, 2000; Heaton et al., 1996; Heaton et al., 1994; Rabkin, McElhiney, Ferrando, VanGorp & Lin, 2004), problems with medication adherence (Albert et al., 1998), and higher risk for mortality (Ellis et al., 1997; Mayeux et al., 1993; Sacktor et al., 1996; Wilkie et al., 1998). Recently, Heaton et al. (2004) reported an association between neuropsychological impairment and poorer performance on functional measures similar to everyday tasks (e.g., shopping, cooking, finances, medication management, and vocational abilities).

In summary, cognitive impairments remain prevalent despite advancements in antiretroviral drug therapies and these symptoms can negatively impact quality of life for individuals with HIV/AIDS.

Prevalence and functional impact of chronic fatigue and depression in HIV/AIDS

Fatigue and mood disturbance (especially depression and anxiety) are often present in many individuals with chronic illnesses, and are identified as the most challenging and debilitating symptoms to manage (e.g., Barroso et al., 2002; Denburg, Carbotte, & Denburg, 1997; Swain, 2000). Chronic fatigue is the most frequently reported symptom of patients with HIV and their health care providers, with estimates ranging from about 20% of asymptomatic individuals with HIV infection to about 40% of adults diagnosed with AIDS (Ferrando et al., 1998; Justice, Rabeneck, Hays, Wu, & Bozzette, 1999). Depression and anxiety are also prevalent in individuals with HIV, with estimates ranging from about 5 to 25% (Ciesla & Roberts, 2001; Grant & Atkinson, 1990). Although depressive symptoms and fatigue are often highly correlated (e.g., Kalichman, Sikkema, & Somlai, 1995; O'Dell, Meighen, & Riggs, 1996; Perkins et al., 1995), fatigue may remain in some individuals even after the alleviation of depressive symptoms (Ferrando et al., 1998). Fatigue and depression in adults with HIV have been associated with poorer quality of life and greater functional limitations, including poorer physical functioning, disability status, and difficulties maintaining employment (e.g., Cleary et al., 1993; Ferrando et al., 1998; Fleishman & Crystal, 1998; Justice et al., 1999; Rabkin et al., 2004).

In summary, many individuals with HIV suffer from psychiatric conditions (especially depressed mood) and chronic fatigue. These debilitating symptoms can affect their daily functioning and consequently their overall satisfaction with life.

Contribution of multiple factors to the manifestation of these symptoms

Given that these symptoms adversely affect quality of life, more attention needs to be directed toward investigating specific factors that may account for the variability in clinical manifestations across individuals with HIV/AIDS.

Cognitive symptoms. A series of ongoing studies conducted at St. Michael's Hospital within the Neurobehavioural Research Unit have aimed to clarify the source and clinical significance of cognitive symptoms in individuals with HIV infection by quantifying the independent contributions of various factors: (a) depressive symptoms; (b) brain functioning (as measured by neuropsychological test performance); (c) medical symptoms; and (d) fatigue. Multiple linear regressions and confirmatory factor analytic approaches have been employed to examine the relations between these symptoms. The following findings are summarized in Figure 1.

Depressive symptoms have consistently accounted for the majority of the variance across various domains of self-reported cognitive symptoms (e.g., memory, language, sensory-motor, and executive problems) (Bassel, Rourke, Halman, & Smith, 2002; Rourke et al., 1999a and 1999b). Other studies have similarly found that depressive symptoms are moderately correlated with subjective cognitive difficulties in adults with HIV/AIDS (e.g., Beason-Hazen, Nasrallah, & Bornstein, 1994; Hinkin et al., 1996; Mapou et al., 1993; Moore et al., 1997; van Gorp et al., 1991; Wilkins et al., 1991).

A recent structural equation modeling study using a sample of 160 adults with HIV infection showed that depression and medical symptoms were highly correlated. Both of these symptoms were also independently associated with overall cognitive symptoms (Carter, Rourke, Murji, Shore, & Rourke, 2003). Millikin, Rourke, Halman,

and Power (2003) also found that fatigue, even after statistically controlling for depressive symptoms, was associated with subjective cognitive symptoms in a group of 68 men with HIV infection.

Some studies using multiple regressions analyses have also found that performance on neuropsychological tests, in particular complex psychomotor efficiency and working memory measures, independently accounted for a significant proportion of the variance across cognitive symptom domains even after the large influence of depression was removed (Bassel et al., 2002; Rourke et al., 1999a). Carter et al. (2003) similarly showed that neuropsychological performance was independently associated with cognitive symptoms, though not correlated with depression and medical symptoms. While some studies have supported this finding (e.g., Beason-Hazen et al., 1994; Lopez, Wess, Sanchez, Dew, & Becker, 1998; Mapou et al., 1993; Poutianinen & Elovaara, 1996), others have failed to obtain an association between self-reported cognitive symptoms and neuropsychological functioning (e.g., Hinkin et al., 1996; Moore et al., 1997; van Gorp et al., 1991). The discrepant findings in the literature may be attributable, at least in part, to variable sample sizes, the breadth and type of cognitive symptoms tapped by questionnaires, and the different domains of neuropsychological functions measured.

Somatic and depressive symptoms. Disruption of physiological processes associated with the invasion and replication of the HIV virus likely contributes to the manifestation of some constitutional symptoms (Fell et al., 1993). Fluctuations in mood, energy level, appetite, and sleep patterns may also arise from prolonged exposure to stressful events or problems with adjusting and coping to life circumstances. Individuals

with HIV often experience significant psychosocial stressors throughout the course of their chronic illness, especially at transition points (e.g., discovery of seropositive status, initiation of HAART medications, or diagnosis of AIDS). Longitudinal studies have identified associations between certain psychosocial characteristics (e.g., stressful life events, denial/avoidance coping style, chronic depression, bereavement, and social isolation) and accelerated disease progression (e.g., Balbin, Ironson, & Solomon, 1999; Cole, Kemeny, Fahey, Zack, & Naliboff, 2003; Kemeny, 2003). Interestingly, some of these studies have also documented accompanying immunological and endocrine changes that may mediate the relation between psychosocial factors and disease progression. For example, Reed, Kemeny, Taylor, and Visscher (1999) noted that individuals with negative expectancies about their prognosis who recently experienced the death of a close friend to AIDS showed increased risk of developing HIV-related somatic symptoms over the next 2.5 to 3.5 years and an accelerated rate of mortality. Declines in CD4 T cell counts and elevations in serum markers of immune activation were observed to accompany this deterioration.

Moreover, a series of studies from the Behavioural Medicine Program at the University of Miami have demonstrated that interventions geared toward managing stress and developing positive coping strategies in individuals with HIV led to improvements in mood along with alterations in neuroendocrine functioning and immunological status (e.g., Antoni, 2003; Antoni et al., 1991; Antoni et al., 2000). These studies suggest that a better understanding of the interaction between psychological and physiological factors may be pivotal to managing depression and fatigue in individuals with HIV infection.

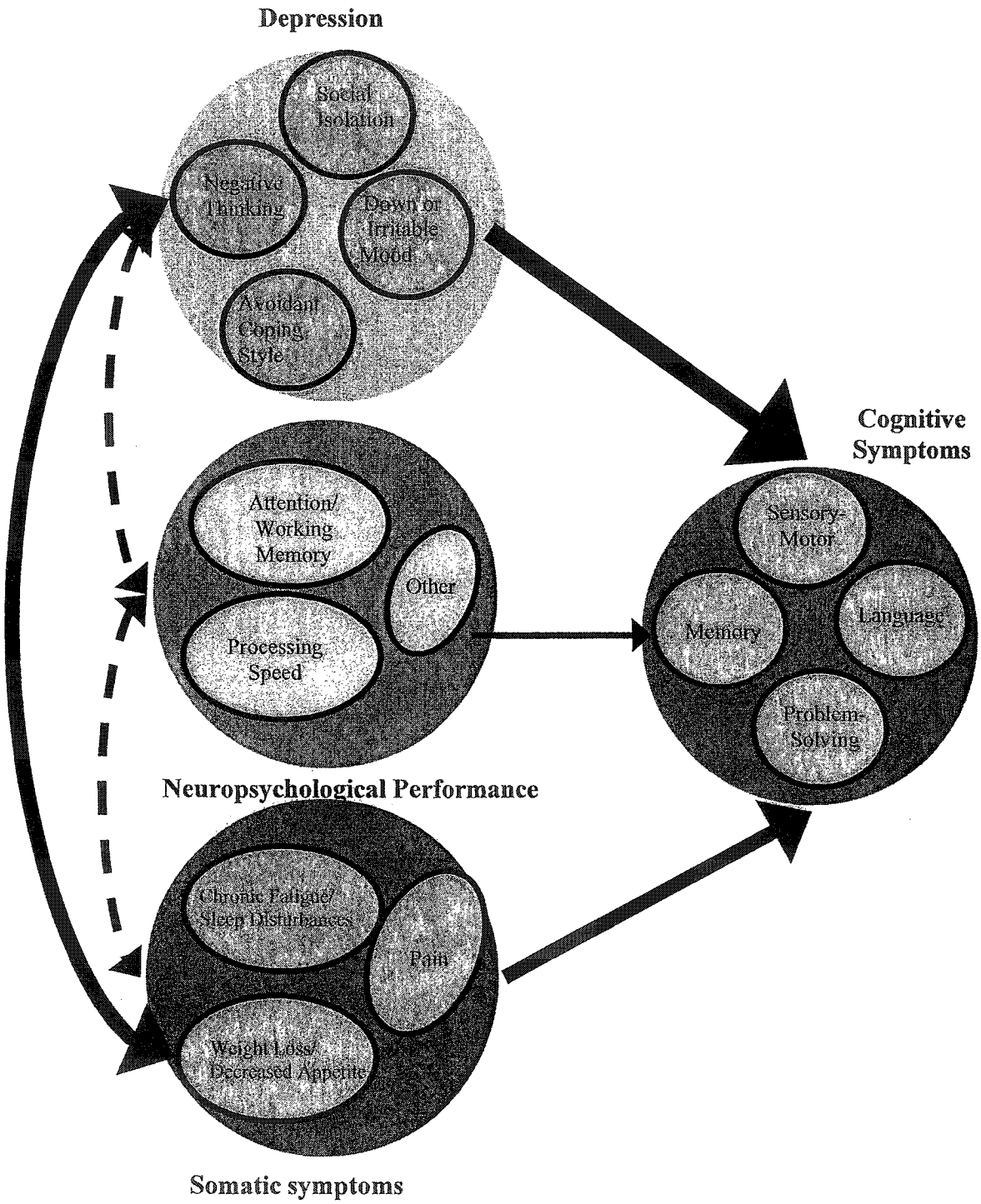

Figure 1. Relations between depression, somatic symptoms, neuropsychological performance, and cognitive symptoms in HIV/AIDS

Note. Solid line = modest to moderate associations between variables
Dotted line = very weak or negligible associations between variables

Biological factors may mediate symptom manifestation: "Illness behaviour"

While depression, fatigue, medical symptoms, and neuropsychological measures of brain functioning are associated with the presence of self-reported cognitive symptoms in some individuals with HIV/AIDS (see Figure 1), a significant proportion of the variability in clinical manifestation remains unexplained. A growing body of evidence within the field of psychoneuroimmunology suggests that systemic alterations in biological processes may mediate some of the somatic, mood, and cognitive changes seen in various immune-based illnesses. The regulation of biological activities is linked by common molecules (cytokines and hormones) and the distribution of their receptors throughout the body. These biological signals act on different tissues, including regions of the brain, to initiate and terminate different physiological and behavioural responses. Functions of the hippocampus, hypothalamus, basal ganglia, and prefrontal cortex connections may be particularly sensitive to fluctuations in cortisol or proinflammatory cytokines due to the high density of receptors located within these brain regions (e.g., Alderson & Novak, 2002; Bethea, Chung, Sapracio, Gillespie, & Benveniste, 1992; Heffelfinger & Newcomer, 2001; Lin, Amaral, Brosnan, & Lee, 1998; Rothwell & Luheshi, 1994). Recent investigations have demonstrated that cytokines can affect neural functioning both locally by their direct presence in brain tissue and systemically through stimulation of cranial nerves and crossing the blood-brain barrier at designated areas (for review see Kronfol & Remick, 2000; Maier, Goehler, Fleshner, & Watkins, 1998; Watkins, Maier, & Goehler, 1995). More specifically, reciprocal inhibitory feedback loops (see Figure 2) involving proinflammatory cytokines (e.g., IL-1, IL-6, and TNF-alpha) and hypothalamic-pituitary-adrenal (HPA) products (e.g., cortisol) are important

for the homeostatic modulation of biological processes induced in response to infection and to physical or psychological stress.

Infection-initiated responses. When the body is invaded with a foreign molecule or pathogen, scavenger immune cells (e.g., macrophages) recognize, engulf, and destroy the invader. This process signals the release of proinflammatory cytokines that act to enhance the immune response by recruiting and activating other immune mechanisms (i.e., cell-mediated and humoral immunity involving T and B lymphocytes). Along with enhancing immune activity, cytokines signal the brain to produce physiological changes that slow down certain activities in order to redirect energy and resources toward other processes necessary for combating infection and promoting recovery (Janeway & Travers, 1997; Maier, Watkins, & Fleshner, 1994). The resultant changes are often collectively referred to as "illness or sickness behaviour:" fever, malaise, fatigue, depressed mood, decreased appetite, accelerated weight loss, increased need for sleep, reduced sex drive, increased sensitivity to pain, and reduced cognitive efficiency (Maier & Watkins, 1998).

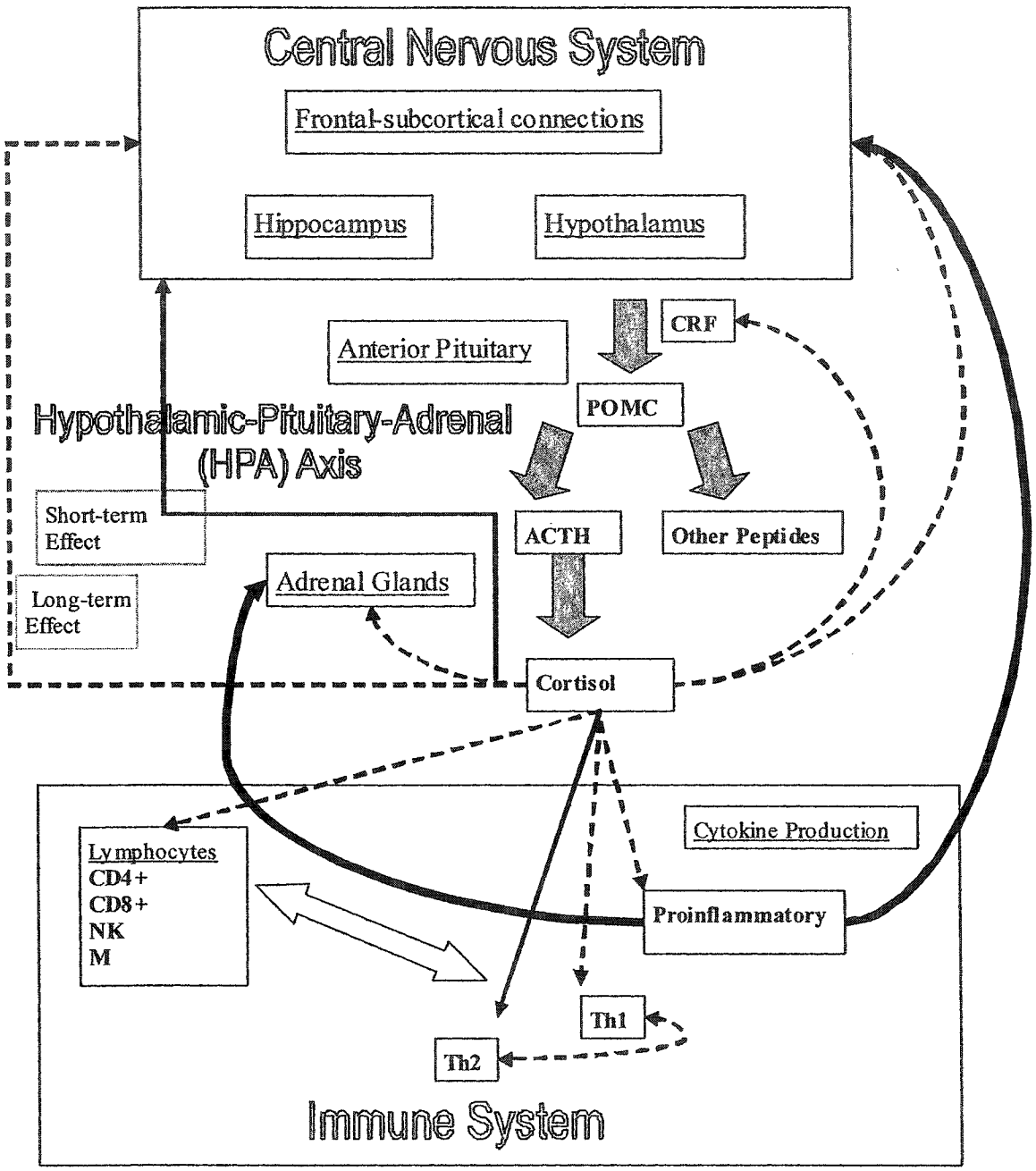

Figure 2. Complex interconnections between the central nervous system, hypothalamic-pituitary axis, and immune system forming a reciprocal inhibitory feedback mechanism that mediates various physiological and behavioural responses.

Note. Solid line = stimulatory effect, Dotted line = inhibitory effect

As proinflammatory receptors tend to be concentrated within the same brain regions responsible for regulating HPA axis responses, immune activation leads to the cascade production of corticotropin-releasing factor (CRF), adrenocorticotropic hormone (ACTH), and glucocorticoids. Stimulation of the HPA axis provides a negative feedback regulatory mechanism to suppress immune responses, preventing cytotoxic immune reactions from getting out of control and causing excessive tissue damage (Decker, Schondorf, Bidlingmaier, Hirner, & von Ruecker, 1996; Elenkov, Papanicolaon, Wilder, & Chrousos, 1996; Marshall et al., 1998). Elevations of various HPA molecules have been associated with modulation of several components of immune responses, including suppression of T-cells, macrophages, and NK cells' function (e.g., Homo-Delarche et al., 1991; Nair, Saravolatz, & Schwartz, 1995; Pawlikowski, Zelazowski, Dohler, & Stepien, 1988) and down-regulating gene transcription and mRNA translation of cytokines (e.g., Bateman, Singh, Kral, & Solomon, 1989; Cupps & Fauci, 1982; Joyce, Steer, & Abraham, 1997; Munck, Guyre, & Holbrook, 1984; Vacca et al., 1992).

Stress-initiated responses. Alternatively, the HPA axis may be initially stimulated in the presence of acute physical or psychological stressors. Activation of brain regions signals the increased production of HPA molecules. The release of glucocorticoids into the bloodstream triggers mobilization of energy sources necessary to respond to the stress, including elevating glucose availability, increasing cardiovascular tone, and enhancing cognition, while limiting other activities such as growth, reproduction, digestion, and immune responses (Alderson & Novak, 2002; Brooke & Sapolsky, 2000). Following the acute onset of a stressful situation, the neuroendocrine system can become sensitized in order to facilitate any subsequent responses to stressors. However,

prolonged exaggerated stress may result in the opposite effect, habituation and decreased reactivity of the HPA axis (Alderson & Novak, 2002; McEwen & Stellar, 1993). Chronic dysregulation of the HPA system may result in reduced appetite, weight loss, lethargy, weakness, gastrointestinal difficulties, and cognitive impairment (Baxter & Tyrell, 1994).

Recent evidence suggests that cytokines and HPA axis hormones may also influence neurotransmitter systems within the brain (for review see Muller & Ackenheil, 1998; Wichers & Maes, 2002). In acute stress situations, both the HPA axis and noradrenergic (NE) systems are initially activated. Subsequent activation of the serotonergic (5-HT) system inhibits these circuits and reduces the stress response. However, prolonged stress may contribute to dysregulation of the HPA axis and imbalanced interactions between NE (hyperactive) and 5-HT (hypoactive) (Ressler & Nemeroff, 2000). Proinflammatory cytokines can further influence neurotransmission by altering the degradation of tryptophan, a precursor to 5-HT. Overstimulation of indoleamine 2,3-dioxygenase (IDO), the enzyme responsible for breaking down tryptophan, by cytokines leads to depletion of plasma concentrations of tryptophan and ultimately a reduction in the synthesis of 5-HT in the brain (Heyes et al., 1992). The disturbances in neurotransmitters accompanying cytokine/HPA activation may further increase an individual's susceptibility to develop depression and declines in cognitive functioning (Widner, Laich, Sperner-Unterweger, Ledochowski, & Fuchs, 2002).

In summary, the intricate connections between cytokine and endocrine messengers, perhaps mediated through alterations in neurotransmitter systems, forms a reciprocal negative feedback mechanism that initiates and controls a wide variety of physiological and behavioural responses. Although transient elevations in cytokines and

hormones are adaptive in managing acute infection or responding to physical and psychological stressors, chronic elevations or deficiencies due to significant disruptions to immune, neural, and/or endocrine activities in certain disease states may disrupt the structural and functional integrity of the other systems and consequently lead to prolongation or exacerbation of certain "illness behaviours" (Brooke & Sapolsky, 2000; McEwen, 2000).

Investigations of biological correlates of fatigue, cognitive symptoms, and depression in healthy controls, medical illnesses, and mood disorders

The pattern of physiological, behavioural, and cognitive alterations associated with dysregulation of proinflammatory cytokine/HPA/neurotransmitter processes resembles some of the symptoms accompanying various immune-mediated illnesses, including those commonly seen in HIV/AIDS. Although cytokine and immune alterations have been implicated in the manifestations of many medical conditions and major depression (Malek-Ahmadi, 1996), their relation to the pathogenesis underlying *specific symptoms* remains to be elucidated. Some preliminary studies have begun to explore the links between systemic biological indicators, fatigue (see Table 1), and cognitive status (see Table 2) in healthy individuals and in patients with various medical conditions. Moreover, new findings support the hypothesis that some individuals suffering from major depression may exhibit alterations in their inflammatory responses (see Table 3) and successful treatment with antidepressants may exert immunoregulatory effects (see Table 4).

Results from the following studies suggest that *systemic immune and endocrine markers* may provide a useful means to monitor biological changes and to investigate their association with overall disease processes as well as with *specific mood, somatic,*

and cognitive symptoms. While diverse methodological approaches and sample characteristics limits the direct comparison of research findings, studies measuring group differences (e.g., mean levels of biological markers in cancer patients with and without depressive symptoms), more so than associations (e.g., correlations between biological markers and the severity of depressive symptoms in cancer patients), have demonstrated links between elevated clinical symptoms and some biological indicators. In particular, fatigue and depressive symptoms were most consistently associated with elevated serum levels of IL-6, TNF-alpha, and neopterin. Although only a few studies have examined the association between cytokine profiles and cognitive symptoms, preliminary findings suggest that IL-6 (and TNF-alpha to a lesser extent) may be useful markers in this regard. Many studies have also documented associations between serum cortisol levels (especially under experimental manipulations), depression, and impaired cognitive functioning.

Healthy adults with immune/HPA activation elicited under experimental conditions. Recent studies from groups in Germany have explored the links between systemic biological indicators (various proinflammatory cytokines and HPA products) and alterations in cognitive, somatic, and mood symptoms in healthy controls. Spath-Schwalbe et al. (1998) examined the effects of systemically administering low doses of IL-6 on mood, sleep, and cognitive symptoms in 16 healthy men. Prolonged increases in plasma concentrations of ACTH and cortisol and a mild rise in body temperature accompanied the induced elevations in IL-6. In comparison with a placebo group, the participants receiving IL-6 subjectively reported more fatigue and trouble with concentrating. Sleep patterns were significantly altered with decreased rapid eye

movements apparent throughout the night. In sleep-deprived (otherwise healthy) males, Vgotzas (1999) also noted that elevated levels of IL-6 corresponded with measures of daytime fatigue.

Reichenberg et al. (2001) investigated the cognitive and behavioural consequences of inducing immune activation in a sample of twenty healthy male volunteers. Elevations in plasma levels of TNF-alpha, TNF-alpha receptors, IL-6, and cortisol levels were reported following the injection of an endotoxin (*Salmonella abortus equi*). Despite limited changes in participants' subjective rating of physical illness symptoms, elevations in TNF-alpha and cortisol plasma concentrations were accompanied by transient increases in anxiety and depressed mood, as well as decreased performance on measures of verbal and nonverbal memory.

Impaired learning and memory (particularly paragraph and word list recall tasks) have also been consistently documented in healthy individuals exposed to experimental conditions designed to elevate their cortisol levels (e.g., Newcomer, Craft, Hershey, Askins, & Bardgett, 1994; Vedhara, Hyde, Gilchrist, Tytherleight, & Plummer, 2000; Wolf, Schommer, Hellhammer, McEwen, & Kirschbaum, 2001). For example, Kirschbaum, Wolf, May, Wippich, and Hellhammer (1996) examined memory performance in conjunction with changes in cortisol levels in two separate samples of healthy individuals. In their first experiment, 13 participants were subjected to a psychological stressor that involved delivering a speech and performing mental math activities in front of an audience. Participants with higher cortisol responses to the stressor performed worse on a word list recall task. In their second experiment, 40 participants were orally given either 10 mg cortisol or placebo pills, and then tested about

an hour later on explicit verbal learning (i.e., cued-recall), implicit verbal learning (i.e., primed word stem completion), and spatial memory tasks (i.e., spatial locations of objects or directions along a path). As compared to those in the placebo group, the participants who were administered the cortisol recalled fewer words during cued-recall and made more errors on the spatial tasks, though no difference in performance was noted across groups for the stem-completion exercise.

Brief single dose treatment may not completely reflect the elevated cortisol levels typically associated with stressful conditions. Newcomer et al. (1999) examined the effects of prolonged durations of hypercorticolemia in healthy volunteers. Administration of cortisol supplements to mimic doses associated with physical and psychological stress over longer periods (4 days) in healthy adults also resulted in poorer recall on a verbal paragraph learning test.

Medical conditions. Elevated levels of proinflammatory cytokines and markers of immune activation (e.g., neopterin) have routinely been used to gauge o*verall disease progression* in various immune-mediated diseases, such as systemic lupus erythematosus (SLE), cancer, Sjogren's syndrome, arthritis, chronic fatigue syndrome, and multiple sclerosis (MS) (e.g., Andrys, Krejsek, Slezak, Drahosova, & Kopecky, 1999; Altingdag, Sahin, Isimer, Akpek, & Kansu, 1999; Giovannoni et al., 1997; Maimone, Gregory, Arnason, & Reder, 1991; Sorensen, 1999; Rentzos et al., 1996; Widner et al., 1999). More recently, studies have begun to explore possible relations between immune mediators and *specific* somatic, depressive, and cognitive symptoms in some of these immune-based medical conditions.

Kurzrock (2001) reviewed possible behavioural implications of proinflammatory cytokines (e.g., anemia, weight loss, night sweats, and pain) that may contribute to cancer-related fatigue. Bower, Ganz, Aziz, and Fahey (2002) reported elevated serum levels of TNF receptors and neopterin, as well as lower serum levels of cortisol in breast cancer 5-year survivors with fatigue as compared with survivors without complaints of fatigue. Acute cancer patients with fatigue prior to commencing radiation treatment had higher IL-6 levels and immune cell counts than acute cancer patients without fatigue (Wratten et al., 2004). In contrast, some studies on radiation-induced fatigue in cancer patients have failed to find associations between levels of fatigue and changes (post-treatment versus baseline) in proinflammatory cytokine levels with radiation (e.g., Ahlberg, Ekman, & Gaston-Johansson, 2004; Geinitz et al., 2001). Discrepant findings may, in part, reflect the diversity of cancer types, disease stages, treatment approaches, and measures.

Elevations in proinflammatory cytokines (TNF-alpha, IL-1, and IL-6) and occasionally cortisol levels have also been associated in some studies of fatigue in individuals with sleep apnea (Vgontzas et al., 2000), acute coronary disease recovering from surgery (Appels, 1999), multiple sclerosis (e.g., Flachenecker et al., 2004), and chronic fatigue syndrome (Buchwald et al., 1997; Cleare et al., 2004; Mullington, Jinze-Selch, & Pollmacher, 2001; Patarca, 2001).

Cytokine-induced behavioural changes also resemble some of the vegetative symptoms associated with depression, including anorexia, weight loss, psychomotor retardation, sleep disturbances, and anergy (Maes, 1993). Musselman et al. (2001) compared plasma concentrations of IL-6 and cortisol levels following dexamethasone

suppression in a group of cancer patients diagnosed with or without comorbid depression. The cancer patients with major depression (n = 8) had markedly higher plasma IL-6 levels than cancer patients without major depression (n = 13) and healthy controls (n = 10). Scores on the depression measure (Hamilton Depression Rating Scale) were positively correlated with cortisol levels, though no association was evident for IL-6 plasma levels. Similarly, elevations in plasma IL-6 concentrations have been described in depressed patients with rheumatoid arthritis (RA) as compared with non-depressed controls without RA or RA patients without depression (Zautra et al., 2004).

Kahl, Kruse, Fahler, Weiss, and Reickmann (2002) examined the association between mRNA TNF-alpha levels, depressive symptoms, and disability status in a group of recently diagnosed patients with MS (n = 16) and demographically matched healthy controls. MS patients demonstrated higher TNF-alpha mRNA expression and depressive symptoms than controls. Depressive symptoms, but not disability status, was positively correlated with TNF-alpha expression both at baseline and 3 to 6 months later.

Although increased levels of proinflammatory cytokines have commonly been reported in multiple sclerosis, fibromyalgia and chronic hepatitis C infection, some studies have failed to find consistent associations between symptom measures of fatigue or depression and systemic markers of inflammatory disease activity (e.g., Gershon, Margulies, Gorczynski, & Heathcote, 2000; Giovannoni, Thompson, Miller, & Thompson, 2001; Gur et al., 2002). However, the majority of these studies examined associations between symptom severity within a single patient group rather than the aforementioned studies that compare conditions with control groups.

Adults with chronic glucocorticoid elevations or deficiencies often demonstrate cognitive impairments, in particular on certain types of learning and memory tasks. Difficulties on explicit memory tasks (e.g., word list or paragraph recall) have been observed in individuals with rheumatoid arthritis who were administered prolonged doses of exogenous glucocorticoids like prednisone (Keenan, Jacobson, Soleymani, & Newcomer, 1995; Keenan et al., 1996). Elevated cortisol levels in patients with depression were positively correlated with problems on tests of verbal memory (Sheline, Wang, Gado, Csernansky, & Vannier, 1996; van Londen et al., 1998). Higher cortisol levels in Alzheimer disease patients were associated with poorer performance on cognitive screening measures (Rasmuson et al., 2001; Umegaki et al., 2000; Weiner, Vobach, Olsson, Svetlik, & Risser, 1997). Moreover, individuals with Cushing's disease often experience cognitive problems and reductions in plasma cortisol levels following treatment has led to some improvements in cognitive functioning, especially on verbal paired-associate learning and recall tasks (Mauri et al., 1993; Starkman et al., 1992).

Much less research is available on the specific cognitive changes mediated by cytokines. Kozora et al. (2001) examined the contribution of IL-6, cortisol, and dehydroepiandrosterone (DHEA) to cognitive impairments in 15 individuals with SLE and 15 individuals with RA. In comparison with 15 age-matched controls, SLE and RA patients performed significantly worse than controls on measures of attention, and SLE patients performed significantly worse than RA and controls on measures of list, paragraph, and figure recall. Cognitive impairments, especially in SLE group, were associated with abnormal levels of DHEA and IL-6 but not cortisol even after controlling for potentially confounding factors such as depression and corticosteroid treatment.

Weaver et al. (2002) investigated the relation between plasma IL-6 and risk for cognitive decline in a sample of 779 elderly men and women. Higher baseline levels of IL-6 were marginally associated with poorer baseline cognitive functioning even after controlling for various demographic, social, and health variables. Individuals with higher baseline levels of IL-6 were also more likely to exhibit cognitive declines at follow-up 2 ½ and 7 years later. In a similar prospective study enrolling 3031 older adults, Yaffe et al. (2003) reported associations between elevated baseline serum IL-6 and cognitive decline at 2-years follow-up. The authors suggested that serum markers of immune activation may provide a practical means to monitor and predict older individuals at-risk for cognitive decline. Recently, Mantovani et al. (2004) examined the significance of serum IL-6 elevations in older adults with cancer. While higher IL-6 was not directly associated with general measures of cognitive status, IL-6 levels did correlate with measures of functional activities of daily living.

Mood disorders. Evidence has recently emerged suggesting that major depression may be accompanied by moderate immune activation. Maes and colleagues (1993, 1995) reported an increase in the plasma concentration and *in vitro* production of IL-1 and IL-6 in patients with Major Depressive Disorder (MDD) in comparison with non-depressed controls. They indicated that increased levels of proinflammatory cytokines correlated with severity of the depressive illness, elevated cortisol, and decreased tryptophan levels. The vast majority of studies reviewed similarly found elevations in plasma concentrations of proinflammatory cytokines (in particular IL-6) in individuals with MDD, dysthymia, and seasonal affective disorder (e.g., Leu, Shiah, Yatham, Cheu, & Lam, 2001; Penninx et al., 2003; Schlatter, Ortuno, & Cervera-Enguix, 2004; Sluzewska et al., 1996; Suarez,

Ranga, Krishnan, & Lewis, 2003; Trzonkowski et al., 2004). Elevated indicators of cell-mediated immunity, including increased monocyte counts and production of neopterin, have also been observed in depressed individuals (e.g., Bonaccorso et al., 1998; Dunbar et al., 1992; Maes et al., 1994).

Selective serotonin reuptake inhibitors (SSRI) and tricyclic antidepressant (TCA) medications have shown immunosuppressant effects both *in vivo* and *in vitro* (for review see Maes, 2001). Animal models have demonstrated inhibitory influences of SSRIs on the production of acute phase proteins and proinflammatory cytokines (Song & Leonard, 1994). An *in vitro* study conducted by Xia, DePierre, and Nassberger (1996) found that various SSRIs and TCAs inhibited proinflammatory cytokine release in samples of stimulated human blood monocytes. However, Kubera et al. (2004) noted that patients with treatment-resistant depression showed increased production of IL-6 in their blood cell samples when antidepressants were added. Prolonged treatment with SSRIs has lead to normalization of serum IL-6 levels in depressed patients relative to controls (Frommberger et al., 1997; Sluzewska et al., 1995). However, many studies have not observed corresponding changes in proinflammatory cytokine levels with short-term antidepressant treatment (e.g., Brambilla et al., 1998; Kubera et al., 2000; Mikova et al., 2001). Study methodology, severity and chronicity of the mood disturbance, durations of therapeutic doses, types of antidepressants, and individuals differences in response to antidepressant treatment may account for some of the discrepant findings. Interestingly, Lanquillon et al. (2000) reported that higher TNF-alpha production by blood mononuclear cells was reduced after a 6-week treatment with amitriptyline in treatment responders, but not in individuals unresponsive to the antidepressant treatment.

Table 1

Selected studies comparing the link between fatigue and biological markers

1st Author (year)	Sample	N_T[a]	N_C[b]	Measure	Lab markers[c]	Group[d]	r[e]
Ahlberg (2004)	Women with uterine cancer undergoing radiation therapy (baseline, 3 wks & after treatment)	15		Multidimensional Fatigue Inventory	Δ IL-1 (s) Δ IL-6 (s) Δ TNF-alpha (s)		ns - ns
Appels (1999)	Acute coronary disease patients with fatigue cf. patients without fatigue	15	15	Self-report exhaustion	IL-1 (s) TNF-alpha (s)	↑ ↑	
Bower (2002)	Breast cancer 5-year survivors with fatigue cf. patients without fatigue	20	20	RAND 36-item Health Survey: Energy/ Fatigue subscale	TNF-receptors (s) IL-1 receptor (s) Neopterin (s) Cortisol (s)	↑ ↑ ↑ ↓	
Buchwald (1997)	Individuals with chronic fatigue cf. standard clinical range	153			CRP (s) Neopterin (s) IL-6	↑ ↑ ns	
Cannon (1999)	Individuals diagnosed with chronic fatigue syndrome cf. controls	6	4	Self-report exertion after 15 minutes exercise	Basal IL-6 (s) Δ IL-6 (s)	↑ ns	ns ns
Cleare (2004)	Individuals with chronic fatigue syndrome without depression cf. controls	16	16		DHEA (s) Cortisol (s)	↑ ↑	
Flachenecker (2004)	Multiple sclerosis patients with fatigue cf. patients without fatigue	26	14	Krupp's Fatigue Severity Scale	IFN-gamma (mRNA) TNF-alpha (mRNA) IL-10 (mRNA)	ns ↑ ns	
Geinitz (2001)	Breast cancer patients during the course of radiation therapy (baseline & 2 months post)	41	41	Fatigue Assessment Questionnaire & Visual Analog Scale on Fatigue Intensity	Δ IL-1 (s) Δ IL-6 (s) Δ TNF-alpha (s)		ns ns ns
Gershon (2000)	Adults diagnosed with Chronic Hepatitis C	78		Fatigue Severity Score	IL-1 (s) IL-6 (s) TNF-alpha (s)		ns ns ns

Giovannoni (2001)	Multiple sclerosis patients	38		Fatigue Questionnaire Scale & Krupp's Fatigue Severity Scale	Neopterin (u) CRP (s)		ns +
Omdal (2002)	Patients with systemic lupus erythematosus	5		Fatigue Severity Scale	IL-2 (s) IL-6 (s) IL-10 (s) TNF-alpha (s)		ns ns ns ns
Patarca (1994)	Patients with chronic fatigue syndrome cf. standard clinical ranges	70			TNF-alpha (s) TNF-beta (s) IL-1 (s) IL-2 (s) IL-2 receptor (s) Neopterin (s)	↑ ↑ ↑ ↑ ↑ ↑	
Spath-Schwalbe (1998)	Healthy men administered low-dose IL-6 cf. placebo	16	16	Self-report fatigue & REM sleep	IL-6 (s) ACTH (s) Cortisol (s)	↑ ↑ ↑	+ + +
Vgontzas (1999)	Healthy males in sleep deprivation experiment	8		Amount and depth of sleep at baseline Daytime sleepiness and fatigue	IL-6 (s)		- +
Vgontzas (2000)	Men with sleep apnea cf. nonapneic matched controls	14	23	Sleep disturbance & daytime sleepiness	TNF-alpha (s) IL-6 (s)	↑ ↑	
Wallace (2001)	Patients with fibromyalgia with fatigue cf. controls	56	56	Self-report fatigue	IL-1 receptor (s) IL-8 (s) IL-6 (stim)	↑ ↑ ↑	
Wratten (2004)	Acute cancer patients starting radiation therapy with fatigue cf. patients without fatigue	21	28	Functional Assessment of Cancer Therapy	IL-6 (s)	↑	+

Note. [a]N_T = sample size for treatment or condition group; [b]N_C = sample size for control group, [c]IL=interleukin, TNF=tumor necrosis factor, IFN = interferon, ACTH = adrenocorticotropic hormone, CRP = C-reactive protein, s = serum levels, u = urinary levels, mRNA= levels of mRNA expression, stim = levels following stimulation of PBMCs with mitogen (LPS/PHA), Δ = change in marker over time; [d] ↑ = elevated levels in condition versus control group, ↓ = lower levels in condition versus control group, ns = non-significant difference between condition and control; [e] + = significant positive correlation (i.e., increased fatigue associated with elevated level of marker), - = significant negative correlation (i.e., increased fatigue associated with low level of marker), ns = non-significant

Table 2

Selected studies comparing the link between cognitive function and biological markers

1st Author (year)	Sample	N_T[a]	N_C[b]	Measures	Lab markers[c]	Group[d]	Assoc[e]
Errico (2002)	Alcoholic males during early withdrawal	18		1. Verbal Memory (Story recall) 2. Cognitive Flexibility (Wisconsin Card Sorting Test)	↑Cortisol (s)		1. - 2. -
Keenan (1995)	Patients with rheumatoid arthritis on prolonged prednisone treatment cf. patients with no treatment	25	25	1. Verbal Memory (Paragraph recall) 2. Non-declarative Memory (Word-stem priming)	↑Cortisol (s)	1. ↓ 2. ns	
Kirschbaum (1996): Experiment 1	Healthy participants exposed to psychosocial stressor (Trier Social Stress Test)	13		Verbal Memory (Recall of 26-item word list)	↑ Cortisol (o)		-
Kirschbaum (1996): Experiment 2	Healthy participants administered cortisol cf. placebo	20	20	1. Verbal Declarative Memory (Cued recall word list) 2. Spatial Memory (park pathway & barn location) 3. Procedural Memory (Word-stem completion task)	↑ Cortisol (s)	1. ↓ 2. ↓ 3. ns	
Kozora (2001)	Patients with Systemic Lupus Erythematosus cf. matched-controls	15	15	Learning Index (Immediate Story Recall, Immediate Figure Recall, & Word List Learning) and Attention Index (Digit Vigilance Test & Paced Auditory Serial Addition Test)	↓ IL-6 (s) ↓ DHEA (s) ns Cortisol (s)		+ + ns
Lupien (1999)	Healthy men with varying doses of hydrocortisone cf. placebo	30	10	1. Working Memory (Item-Recognition Task) 2. Verbal Declarative Memory (Recall of Word Pairs)	↑ Cortisol (s)	1. ↓ 2. ns	
Mantovani (2004)	Older adults with cancer	84		1. Cognitive Status 2. Functional Activities of Daily Living	↑ IL-6 (s)		ns -
Mauri (1993)	Cushing's syndrome patients cf. matched controls	25	25	Verbal Memory (Paragraph recall & Paired associates learning tasks)	↑Cortisol (s)	↓	-

Newcomer (1994)	Healthy adults administered dexamethasone cf. placebo	10	9	Verbal Memory (Immediate & Delayed Paragraph Recall)	↓ Cortisol (o, dex supp)	↓	
Newcomer (1999)	Healthy participants administered low and high doses of cortisol for 4 days cf. placebo group	31	20	Verbal Memory (Immediate and Delayed Paragraph Recall)	↑ Cortisol (s)	↓	
Rasmuson (2001)	Women with Alzheimer disease cf. young & older healthy women	10	14	Clinical Dementia Rating Scale	↑ Cortisol metabolites (u)	↓	
Reichenberg (2001)	Healthy males injected with an endotoxin cf. placebo	20	20	Verbal Memory (Story Recall & List Learning) and Visual Memory (Figure Recall)	↑ TNF-alpha (s) ↑ Cortisol (s) ↑ IL-6 (s)	↓ ns ↓	
Sheline (1996)	Depressed patients cf. matched controls	10	10	Verbal Memory (Paragraph recall & List learning)	↑Cortisol (s)	↓	
Spath-Schwalbe (1998)	Healthy men administered low-dose IL-6 cf. placebo	16	16	Self-report difficulties with concentration	↑ IL-6 (s) ↑ ACTH (s) ↑ Cortisol (s)	↓ ↓ ↓	+ + +
Starkman (1992)	Cushing's syndrome patients	12		Verbal Memory (Paragraph recall & Paired Associates Learning tasks)	↑Cortisol (s)		-
Umegaki (2000)	Patients with Alzheimer disease and vascular dementia cf. control elderly	94	21	Mini Mental Status Examination	↑Cortisol (s)	↓	-
Van Londen (1998)	Depressed patients cf. non-depressed controls	15	15	Verbal Memory (Paragraph recall & List learning)	↑Cortisol (s)	↓	-
Vedhara (2000)	Students during exam periods cf. students during non-exam periods	60	60	1. Attention (Test of Everyday Attention) 2. Verbal Memory (Primacy Effect for 20-item Word List) 3. Verbal Memory (Immediate Recall)	↓ Cortisol (o)		1. + 2. + 3. -
Weaver (2002)	Older adults	779		Modified Mini Mental Status Examination (Cognitive status at 2½ and 7 yrs follow-up)	↑ IL-6 (s) at baseline		-
Weiner (1997)	Patients with Alzheimer disease	9		Modified Alzheimer Disease Assessment Scale-Cognitive (Change score from baseline to 2.5 years)	↑Cortisol (s): baseline		+

Widner (2000)	Patients with Alzheimer disease cf. similar aged controls	21	20	Mini Mental Status Examination	↓ Tryptophan (s)		+
Wolf (2001)	Healthy participants exposed to psychosocial stressor (Trier Social Stress Test) cf. controls	22	36	Verbal Learning (Immediate Recall of Word List)	↑ Cortisol (o): men ↑ Cortisol (o): women	ns ns	- ns
Wolkowitz (1990)	Depressed patients	21		Verbal Memory (Word list recognition task)	↑Cortisol (s, dex supp)		-
Yaffe (2003)	Older adults	3031		Modified Mini Mental Status Examination (Cognitive status at 2-year follow-up)	At Baseline: ↑ IL-6 (s) ↑ CRP (s) ↑ TNF-alpha (s)		 - - ns

Note. [a]N_T = sample size for treatment or condition group; [b]N_C = sample size for control group; [c]IL=interleukin, TNF=tumor necrosis factor, ACTH = adrenocorticotropic hormone, DHEA = dehydroepiandrosterone, CRP = C-reactive protein, s = serum levels, o = saliva levels, dex sup= serum levels under conditions of dexamethasone suppression, ↑ = elevated levels, ↓ = low levels; [e] ↑ = poorer performance on test in condition versus control group, ns = no difference between condition and control performance; [f] + = positive correlation between performance and serum levels, - = negative correlation between performance and serum levels, ns = association not significant

Table 3

Selected studies comparing the link between depression and biological markers

1st Author (year)	Sample[a]	N_T[b]	N_C[c]	Diagnosis[d]	Measure	Lab markers[e]	Group[f]	r[g]
Anisman (1999)	Patients with MDD or dysthymia cf. non-depressed controls	27	27	DSM-IIIR/ DSM-IV		IL-1 (stim) IL-2 (stim) ACTH (s) Cortisol (s) NE (s)	↑ ↓ ↑ ↓ ↑	
Appels (2000)	Patients with coronary artery disease with depressive symptoms/exhaustion cf. patients without depressive symptoms/exhaustion	15	15		Self-report depression/ exhaustion	IL-1 (mRNA) TNF-alpha (mRNA)	↑ ↑	
Bonaccorso (1998)	Patients with MDD cf. normal controls	10	17	DSM-IIIR		Neopterin (u)	↑	
Brambilla (1998)	Elderly women with MDD (inpatients) cf. matched controls	10	20	DSM-IIIR	Hamilton Depressing Rating Scale	IL-1 (s) IL-6 (s) TNF-alpha (s)	ns ns ns	ns ns ns
Carpenter (2004)	Patients with MDD cf. matched controls	18	26	DSM-IV		IL-6 (csf)	ns	
Frommberger (1997)	Patients with MDD cf. healthy controls (*acute MDD vs. **MDD in remission)	12	12	DSM-IIIR	Montgomery Asberg Depression Rating	IL-6 (s)	↑ (*) ns (**)	
Glaser (2003)	Older adults	119			Beck Depression Inventory	IL-6 (s)		+
Gur (2002)	Patients with Fibromyalgia and depressive symptoms cf. healthy controls	81	32		Hamilton Depression Rating Scale	IL-1 (s) IL-2 receptor (s) IL-6 (s) IL-8 (s)	ns ↑ ns ↑	
Gur (2004)	Patients with fibromyalgia (FM) and chronic fatigue syndrome cf. healthy controls	130	46		Beck Depression Inventory	Cortisol (s)	↓	- (esp FM)

Kahl (2002)	Multiple sclerosis patients cf. healthy controls	16	10		Beck Depression Inventory	TNF-alpha (mRNA) INF-gamma (mRNA) IL-10 (mRNA) IL-4 (mRNA)	↑ ↑ ↑ ns	+ + + ns
Leu (2001)	Patients with Seasonal Affective Disorder cf. matched normal controls	15	15			IL-6 (s) IL-6 receptor (s) IL-2 receptor (s)	↑ ns ns	
Maes (1995)	Patients with MDD (acute and chronic remission) cf. healthy controls	77	38	DSM-IIIR	Hamilton Depression Rating Scale	IL-6 (s) IL-6 receptor (s) IL-2 receptor (s)	↑ ↑ ↑	
Maes (1997)	Patients with MDD (including treatment-resistant depression) cf. non-depressed controls	35	15	DSM-IIIR	Hamilton Depression Rating Scale	IL-1 receptor (s) Il-6(s)	↑ ↑	ns ns
Mikova (2001)	Patients with MDD cf. controls	28	15	DSM-IV		IL-6 (s) IL-8 (s) TNF-alpha (s) IL-2 receptors (s)	↑ ns ↑ ns	
Musselman (2001)	Cancer patients with comorbid MDD cf. cancer patients without depression	8	13	DSM-IIIR	Hamilton Depression Rating Scale	IL-6 (s) Cortisol (s, dex sup)	↑ ↑	ns +
Natelson (1999)	Patients with chronic fatigue syndrome and comorbid MDD cf. healthy controls	30	87	DSM-IIIR	Centers for Epidemiological Study-Depression	IL-1 (mRNA) IFN-gamma (mRNA) IL-2 (mRNA) IL-4 (mRNA) IL-6 (mRNA) IL-10 (mRNA) IL-12 (mRNA) TNF-alpha (mRNA)	↓ ns ns ns ns ns ns ns	
Penninx (2003)	Elderly adults with depressive symptoms cf. normal controls	145	2879		Centers for Epidemiological Study-Depression	IL-6 (s) TNF-alpha (s) CRP (s)	↑ ↑ ↑	
Reichenberg (2001)	Healthy males injected with an endotoxin	20			Depression Adjectives Check List	TNF-alpha (s) Cortisol (s) IL-6 (s)		+ + +

Schlatter (2004)	Patients with MDD or dysthymia cf. healthy controls	22	15	DSM-IIIR	Hamilton Depression Rating Scale	IL-1 (stim) IL-6 (stim) TNF-alpha (stim)	↑ ↑ ns	ns ns ns
Sluzewska (1996)	Inpatients with MDD cf. non-depressed controls	49	15	DSM-IIIR	Hamilton Depression Rating Scale	IL-6 (s) IL-6 receptor (s) IL-2 (s) CRP (s)	↑ ↑ ↑ ↑	ns ns ns ns
Starkman (1992)	Patients with Cushing's disease	11			Hamilton Depression Rating Scale	ACTH (s, dex sup)		+
Suarez (2003)	Non-smoking healthy men	53			Beck Depression Inventory	IL-1 (stim) TNF-alpha (stim) IL-8 (stim)		+ + +
Trzonkowski (2004)	Elderly with MDD cf. non-depressed controls	10	10	DSM-IV		TNF-alpha (s) IL-6 (s) ACTH (s) Cortisol (s)	↑ ↑ ↓ ↑	
Zautra (1994)	Individuals with rheumatoid arthritis	33			Beck Depression Inventory	Cortisol (s) Prolactin (s)		ns +
Zautra (2004)	Rheumatoid arthritis (RA) patients with comorbid MDD cf. RA patients without depression and healthy controls	45	106	DSM-IV		IL-6 (s)	↑	

Note. [a] MDD=major depressive disorder; [b] N_T = sample size for treatment or condition group; [c] N_C = sample size for control group, [d] DSM = Diagnostic and Statistical Manual of Mental Disorders; [e] IL=interleukin, TNF=tumor necrosis factor, ACTH = adrenocorticotropic hormone, CRP = C-reactive protein, IFN = interferon, NE = norepinephrine, s = serum levels, csf= cerebral spinal fluid levels, u = urinary levels, dex sup= serum levels under conditions of dexamethasone suppression, mRNA= levels of mRNA expression, stim = levels following stimulation of PBMCs with mitogen (LPS/PHA); [f] ↑ = elevated levels in condition versus control group, ↓ = lower levels in condition versus control group, ns = non-significant difference between condition and control groups; [g] + = significant positive correlation (i.e., increased severity of depression associated with elevated level of marker), - = significant negative correlation (i.e., increased severity of depression associated with low level of marker), ns = non-significant

Table 4

Selected studies investigating the effects of antidepressants on biological indicators

1st Author (year)	Sample[a]	N_T[b]	N_C[c]	Treatment	Duration	Lab markers[d]	Group[e]	Change[f]
Brambilla (1998)	Elderly women with MDD (inpatients) cf. matched controls	10	20	Phosphatidylserine	30 days	IL-1 (s) IL-6 (s) TNF-alpha (s)	ns ns ns	ns ns ns
Kubera (2000)	Patients with MDD cf. non-depressed controls	9	10	Unspecified antidepressants	6 weeks	IL-1 receptor (s) IL-6 (s) IL-10 (s)	↑ ↑ ↑	ns ns ns
Kubera (2004)	Treatment-resistant depressed patients cf. controls	7	19	Imipramne, venlafaxine, L-5-HT, or fluoxetine		IL-6 (stim) TNF-alpha (stim)	↑ ns	
Lanquillon (2000)	Inpatients with MDD cf. controls (*non-responders **responders)	24		Amitryptiline	6 weeks	IL-6 (s) TNF-alpha (s)	↑(*) ↑ (both)	ns ↓(**)
Maes (1995)	Patients with MDD (acute and chronic remission) cf. healthy controls	77	38	Mixed sample (fluoxetine, nortiptyline, amitryptiline, or imipramine)	81.2+/-38.3 days	IL-6 (s) IL-6 receptor (s) IL-2 receptor (s)	↑ ↑ ↑	ns ns ns
Maes (1997)	Patients with MDD (including treatment-resistant depression) cf. non-depressed controls	35	15	Trazodone alone, Trazadone with pindolol or Trazadone with fluoxetine	5 weeks	IL-1 receptor (s) IL-6(s) IL-6 receptor (s)	↑ ↑ ↑	ns ns ↓
Maes (1999)	Normal healthy adults	9		Clomipramine, sertraline, or trazadone		IFN-gamma (stim) IL-10 (stim)	↓ ↑	
Mikova (2001)	Patients with MDD cf. controls	14	15	Mixed sample (clomipramine, paroxetine, mianserin, or amitriptyline)	6 weeks	IL-6 (s) IL-8 (s) TNF-alpha (s) IL-2 receptors (s)	↑ ns ↑ ns	ns ns ns ns
Weizman (1994)	Patients with MDD cf. matched healthy controls	10	10	Clomipramine	4 weeks	IL-1 (stim) IL-2 (stim) IL-3 (stim)	↑ ↑ ↑	
Xia et al. (1996)	Normal healthy adults	4		Clomipramine, imipramine or citalopram		IL-2 (stim) IFN-gamma (stim) TNF-alpha (stim) IL-6 (stim)	↓ ↓ ↓ ↓	

Note. [a] MDD=major depressive disorder; [b]N_T = sample size for treatment or condition group; [c]N_C = sample size for control group; [d]IL=interleukin, TNF=tumor necrosis factor, IFN= interferon, s = serum levels, stim = levels following stimulation of PBMCs with mitogen (LPS/PHA); [e] ↑ = elevated levels in condition versus control group, ↓ = lower levels in condition versus control group, ns = non-significant difference between condition and control group; [f] ↓ = reduced levels over time with treatment, ns = no significant changes in levels over time with treatment

Potential neural correlates of "illness behaviour"

Given the higher density of proinflammatory cytokine and hormonal receptors located within the hypothalamus, hippocampus, basal ganglia, and prefrontal cortex connections, functions of these brain regions may be more susceptible to cytokine/HPA-induced activity. For brevity and readability the hypothesized functions of these brain structures are reviewed, though it is recognized that these structures do not function in isolation but rather operate as part of comprehensive pathways within the brain.

The multiple nuclei within the hypothalamus form intricate connections with diverse regions of the brain, including the brain stem, anterior thalamus, limbic cortex, hippocampus, and pituitary gland. Stimulation and lesion studies have shown that the hypothalamus is pivotal for the integrated control and maintenance of many different physiological activities, such as regulation of arterial pressure and heart rate, body temperature, sleep-wakefulness cycles, water conservation, hunger sensation, sexual drive, pain perception, and emotional control (Guyton, 1991). The hypothalamus co-ordinates bodily functions in a rhythmic fashion (daily and seasonal cycles) as well as spontaneously in response to internal and external factors (Overeem et al., 2002).

The medial temporal lobe system is comprised of the hippocampus and adjacent cortical regions. Bidirectional projections exist between the hippocampus and entorhinal cortex. The entorhinal cortex forms reciprocal projections with parahippocampal and perirhinal cortices, as well as sends and receives information from orbitofrontal, cingulate, superior temporal gyrus, and insular cortices. The parahippocampal and perirhinal cortices have more widespread reciprocal connections with unimodal and polymodal association areas in frontal, temporal, and parietal lobes (Squire, 1992; Squire,

Stark, & Clark, 2004). The integrity of the hippocampus and related structures has been linked to learning and memory. Convergent support comes from numerous lesion and imaging studies in rats, nonhuman primates, and humans (for detailed reviews see Eichenbaum, 1999; Lepage, Ghaffar, Nyberg, & Tulving, 2000; Squire, 1992; Squire, Knowlton, & Musen, 1993; Squire et al., 2004; Tulving & Markowitsch, 1998). In particular, declarative memory (also referred to as explicit, relational, contextual, or configurational memory) that involves the formation of relationships, transfer of newly acquired information to long-term storage, and recalling facts or events over short periods of time may be mediated by the medial temporal lobe system. The role of the hippocampal structures in learning and memory storage is thought to be temporary, such that memory gradually reorganizes so that permanent storage occurs in the neocortex (Squire, 1992; Squire et al., 2004). Following consolidation and more permanent storage of new information, retrieval of this information is thought to involve extra-hippocampal structures including the frontal cortex (Squire et al., 1993).

The frontal-subcortical circuitry are highly complex and mediate a wide range of behaviours and motor activity. A series of five parallel circuits linking specific regions of the frontal cortex to the striatum, globus pallidus, and thalamus have been described (e.g., Alexander, DeLong, & Strick, 1987; Cummings, 1993; Tekin & Cummings, 2002). The *motor circuit*, originating in the supplementary motor area, premotor cortex, and motor cortex, is responsible for initiating and sequencing multiple successive and parallel muscle movements to achieve desired goals. The *oculomotor circuit* originates from the frontal eye field and posterior parietal cortex, and mediates the complexity of eye movements. The *dorsolateral prefrontal circuit* is thought to be involved in cognitive

tasks, such as planning, organization, regulating behaviours, shifting sets, and solving novel problems. Personality changes, behavioural disinhibition, and emotional lability may result from disruption of the *lateral orbitofrontal circuit*. The *anterior cingulate circuit* is thought to be important for motivation, such that lesions in this pathway result in apathy, indifference, and lack of motor and verbal initiation (for detailed review see Tekin & Cummings, 2002).

The neuropathology of HIV: At system, cellular, and molecular levels

Brain regions. Neuroradiology and pathology studies provide support for the potential disruption of both medial temporal and frontal-subcortical brain systems in HIV. Post-mortem analyses of individuals with AIDS often reveal cerebral atrophy with sulci widening and ventricular dilation (e.g., Poutiainen et al., 1993; Vago, Trabattoni, Lechi, Cristina, & Budka, 1990). Central white matter lesions and loss of specific subpopulations of neurons found within the basal ganglia, hippocampus, and frontal-temporal cortex are frequently observed (e.g., Bell, 1998; Gendelman et al., 1994; Wiley et al., 1991). For example, Reyes, Mohar, Mallory, Miller, and Masliah (1994) described neuronal atrophy and astrogliosis of the hippocampal formation, basal ganglia, and frontal cortex in 11 out of 19 autopsies of individuals with AIDS. High HIV viral DNA loads were also found in the medial temporal lobe region during post-mortem analyses of eight patients diagnosed with AIDS-related dementia (Fijumura et al., 1997). Petito, Roberts, Cantando, Rabinstein, and Duncan (2001) recently described neuronal loss, increased astrocyte gliosis, and the presence of high levels of cytokine co-receptors in hippocampal regions based on autopsies of 22 adults with AIDS.

Similarly, structural imaging studies have documented diffuse cerebral atrophy, widening cortical sulci, enlarged ventricles, and periventricular white matter abnormalities in some individuals with HIV infection and AIDS (Elovaara et al., 1990; Raininko et al., 1992). Oberfield et al. (1994) noted the presence of hippocampal atrophy on 8 out of 15 CT scans of children with HIV infection. Decreased volume of the basal ganglia has also been observed and correlated with increased cognitive impairments (e.g., Aylward et al., 1993; Aylward et al., 1995; Hestad et al., 1993). Harrison et al. (1998) reported that the presence of white matter abnormalities on MRI scans was associated with poor overall neuropsychological performance and more specifically, declines on tests of executive functioning, psychomotor speed, and nonverbal memory.

Moreover, abnormal regional blood flow in temporal and frontal regions has been documented in patients with HIV infection relative to controls using both functional magnetic resonance imaging and positron emission tomography imaging scans (e.g., Chang, Ernst, Leonido-Yee, & Speck, 2000; van Gorp et al., 1992; Wiseman et al., 1999). More marked abnormalities have been correlated with more advanced disease stage, lower CD4 T cell counts, higher viral loads, and increased cognitive impairments (e.g., Chang, Ernst, Leonido-Yee, & Speck, 2000; Chang et al., 2002; Hall, Whaley, Robertson, & Hamby, 1996).

Biological mechanisms. Progressive impairments in immune and CNS functioning in individuals with HIV are thought to result from both direct and indirect destruction of cells during the viral replication process (Gorman & Kertzner, 1990). The HIV virus has a predilection for cells with CD4 receptors (i.e., CD4 T lymphocytes, macrophages, and microglial cells). Macrophages are thought to be responsible for

transporting HIV across the blood brain barrier and have been shown to enter the CNS within days to weeks of infection (e.g., Davis et al., 1992; Resnick, Berger, Shapshak & Tourtellotte, 1988). However, HIV does not seem to directly infect neurons or oligodendrocytes but instead reservoirs of virus are stored within brain macrophages, microglia, and multinucleated giant cells (e.g., Gendelman et al., 1994; Minagar et al., 2002; Orenstein, 2001). Chronic low-grade activation of macrophages and microglia by HIV results in the release of a cascade of neurotoxic viral (e.g., protein gp120) and/or cellular factors (e.g., proinflammatory cytokines, nitric oxide, oxygen radicals, prostaglandins, or leukotrienes) that can cause secondary damage to surrounding tissue (e.g., Brenneman, McCune, Mervis, & Hill, 1994; Gendelman et al., 1994; Minagar et al., 2002).

Excess production of proinflammatory cytokines (most notably TNF-alpha) may have multiple adverse effects on their own: (1) stimulate microglia and astrocytes to produce additional neurotoxins such as arachidonic metabolites, quinolinic acid, and nitric oxide (Genis et al., 1992; Wesselingh et al., 1994; Pemberton, Kerr, Smythe, & Brew, 1997); (2) inhibit astrocytes from buffering extracellular glutamate which is also neurotoxic in excess amounts (Fine et al., 1996); (3) enhance HIV infection of host cells and viral replication processes (Alfano & Poli, 2001; Merrill & Chen, 1991; Vyakarnam, McKeating, Meager, & Beverley, 1990); and (4) stimulate production of adhesion molecules and chemokines (MCP-1) that alter permeability of the blood brain barrier to immune cells (Fiala et al., 1997; Nottet et al., 1996).

The HIV virus may stimulate the HPA axis directly via the production of peptide sequences similar to pituitary regulatory hormones (e.g., ACTH) or indirectly by

cytokines enhancing CRF secretion (Corley, 1995; Sapolsky, Rivier, Yamamoto, Plosky, Vale, 1987; Smith & Blalock, 1982; Woloski et al., 1985). Elevated cortisol levels and HPA axis imbalances, regardless of their aetiology, may hasten the progression of HIV infection by suppressing cell-mediated immune functioning and the production of Type 1 cytokines (Clerici et al., 1997b; Corley, 1995; Rook, Onyebujon, & Stanford, 1993; Sapse, 1997). Interestingly, glucocorticoids may also further exacerbate the neurotoxic effects of gp120. A synergistic increase in neuronal death was apparent in cultures of hippocampal, cortical, and striatal tissues from rats when both gp120 and corticosterone (similar to cortisol in humans) were present (Brooke, Chan, Howard, & Sapolsky, 1997; Iyer, Brooke, & Sapolsky, 1998). Brooke and Sapolsky (2000) hypothesized that both gp120 and glucocorticoids contributed to neuronal death by altering different aspects of cellular metabolism, and together accelerating the depletion of energy sources.

Although the exact mechanism by which HIV damages neurons is still unknown, these findings suggest that damage to brain systems may stem from *death* of neurons, *disruption* of neuronal functioning, and/or *modification* of neurotransmitter systems (Adle-Biassette et al., 1999; Bell, 1998; Everall et al., 1999) indirectly mediated through factors released from proximal virus-infected macrophages and microglia (Gendelman et al., 1994; Minagar et al., 2002). Neuronal destruction may be further amplified by the interaction and perpetuation of immune and endocrine molecules via positive feedback loops. Central white matter and deep grey matter are often characterized by infiltration of macrophages containing HIV virus, astrogliosis, and the development of microglial nodules and multinuclear giant cells (i.e., fused macrophages and/or glial cells often containing copious amounts of virus and surrounded by ineffective T cells) (Gendelman

et al., 1994). The presence of multinuclear giant cells has been correlated with the degree of dementia (McArthur et al., 1999). As outlined above, the disruption of certain brain systems (hypothalamic, medial temporal, and frontal-subcortical) may contribute to somatic, cognitive, and depressive symptoms in some individuals. Consequently, it may be useful to examine whether individual differences in immune and endocrine functioning is associated with the presence of these symptoms in HIV. The present study selected systemic indicators reflective of different aspects of this mechanism: (1) HIV replication and disease status (CD4 T cell counts and viral load); (2) macrophage activation and cytotoxicity (neopterin); (3) proinflammatory cytokines (IL-6 and TNF-alpha); and (4) cortisol. Previous research in HIV on each of these measures will be reviewed in turn.

I. CD4 T cells and Viral Load: Studies have extensively documented the development of clinical symptoms and AIDS conditions following rapid declines in CD4 T cells (Detels et al., 1987; Fahey et al., 1990). Although decline in CD4 T cell counts has served as the hallmark for disease progression (Fahey et al., 1998; Pantaleo et al., 1993; Staszewski, DeMasi, Hill, & Dawson, 1998), relatively weaker associations have been reported between CD4 T cell counts and cognitive impairments in HIV/AIDS (Bornstein et al., 1991; Dal Pan et al., 1998).

Increased levels of viral load in cerebrospinal fluid (CSF) and plasma have also been correlated with the rate of CD4 T cell decline, poorer prognosis, and increased clinical disease stages in HIV/AIDS (Hogervorst et al., 1995; Mellors et al., 1997). Some studies have also reported a link between elevations in viral load and cognitive impairment, especially for individuals diagnosed with AIDS dementia (Brew, Pemberton,

Cunningham, & Law, 1997; Buffet et al., 1991; Farzadegan et al., 1992; Kim et al., 2001; Royal, Selnes, Concha, Nance-Sproson, & McArthur, 1994; Singer et al., 1994). However, other studies have not found an association between plasma viral load and cognitive decline in HIV infection (Dal Pan et al., 1998; Robertson et al., 1998). Ellis et al. (1997) suggested that higher CSF viral load may only reflect increased risk of cognitive impairments when significant corresponding declines in CD4 T cell counts are also evident. Childs et al. (1999) compared the predictive value of both plasma viral load and CD4 T cell counts as markers of dementia and sensory neuropathy in a sample of 1604 men with HIV infection over a 10 year period. Individuals with high plasma viral loads had an 8.5 fold greater risk of developing dementia and 2.3 fold greater risk of developing sensory neuropathy. Similarly, lower CD4 T cell counts were associated with a 3.5 fold greater risk for dementia and 1.4 fold greater risk for sensory neuropathy.

II. Neopterin: Neopterin is a compound derived from guanosine triphosphate that is released from macrophages following activation. High concentrations of neopterin are associated with production of reactive oxygen species. Hence, neopterin can serve as a marker of the level of macrophage activation and an estimate of the extent of oxidative stress in the immune system (Hamerlinck, 1999; Murr, Widner, Wirleitner, & Fuchs, 2002).

Neopterin is markedly elevated upon initial infection with HIV. Levels of neopterin tend to decline somewhat after seroconversion, though they remain elevated in more than 75% of individuals with HIV in asymptomatic stages and progressively increase with advancing disease stages (Baier-Bitterlich, Wachter & Fuchs, 1996; Fahey et al., 1990; Fuchs et al., 1989). Metha et al. (1996) reported that CSF levels of neopterin

progressively increased with advanced disease stages based on a subsample of 377 participants from the San Diego HIV Neurobehavioural Research Center study. Decreases in serum neopterin levels have also been documented after initiation of HAART regimens (Amirayan-Chevillard et al., 2000; Stylianou, Aukrust, Bendtzen, Muller, & Froland, 2000; Zangerele et al., 2002).

Griffin et al. (1991) examined serum and CSF concentrations of neopterin in 121 individuals with HIV infection and 62 HIV-negative controls. Levels of neopterin were higher in individuals with HIV infection than the controls, and especially elevated in HIV-positive individuals with neurological diseases, such as HIV associated meningitis, opportunistic infections, and inflammatory demyelinating polyneuropathologies. CSF and serum neopterin levels have also been correlated with measures of increased blood brain barrier permeability (albumin ratio) in HIV-infected individuals at different stages of disease (Andersson, Hagberg, Fuchs, Svennerholm, & Gisslen, 2001).

III: IL-6 and TNF-alpha: Peripheral proinflammatory cytokines are involved in the initiation of localized and systemic immune responses, such as activation of liver cells to synthesize proteins necessary for other immune responses or vasodilation of blood vessels to increase their permeability for proteins and immune cells at the infection site (Janeway & Travers, 1997). They also monitor and modulate biological processes within the periphery by both directly and indirectly communicating with the CNS (for review see Maier & Watkins, 1998). Proinflammatory cytokines directly produced in the brain are thought to have pivotal roles in protecting neurons and mediating inflammation. However, both prolonged elevations and deficient levels can be detrimental to CNS functioning (Wang et al., 2002).

Plasma levels of proinflammatory cytokines (IL-1, IL-6, and TNF-alpha) are often elevated in HIV disease, especially among patients with opportunistic infections (Valdez & Lederman, 1997-1998). Peripheral blood mononuclear cells isolated from patients with HIV have been shown to spontaneously release high levels of IL-1, TNF-alpha and IL-6, and increased release was correlated with advanced stages of HIV-1 infection (Berman, Zaldivar, Imfled, Kenney, & Sandborg, 1994; Honda et al., 1990; Roux-Lombard, Modoux, Cruchaud, & Dayer, 1989; Wright, Jewett, Mitsuyasu, & Bonavida, 1988). Although an *in vivo* study conducted by da Silva, Singer, Fong, and Ottaway (1999) found no differences in TNF-alpha and IL-6 levels at baseline, greater increases in serum TNF-alpha and IL-6 levels were evident after experimental challenge with lipopolysaccharide in individuals with HIV infection ($n = 29$) than in control subjects ($n = 15$).

Higher TNF-alpha and soluble TNF receptor concentrations in plasma were associated with increased disease progression, lower CD4 and CD8 T lymphocyte counts, and higher HIV mRNA levels (Aukrust et al., 1994; Godfried et al., 1994; Kulinkovich et al., 1992). Ryan et al. (2001) reported that higher levels of soluble TNF-alpha receptors in serum were correlated with the presence of cognitive impairment and brain atrophy on MRI scans in a sample of 28 individuals with HIV infection. Increased serum TNF-alpha was also noted in a sample of individuals with HIV encephalopathy as compared with HIV positive individuals without neurological disease (Grimaldi et al., 1991), and in samples of AIDS patients with dementia, vacuolar myeopathy, and sensory neuropathy as compared with AIDS patients without neurological disease (Wesselingh, Glass, McArthur, Griffin, & Griffin, 1994).

Similar elevations in TNF-alpha have been observed in CSF fluid of individuals with HIV infection as compared with HIV negative controls (Grimaldi et al., 1991; Tyor et al., 1992). However, these studies did not confirm the correlation between TNF-alpha levels and the presence of CNS disease.

Although some studies have demonstrated a positive correlation for IL-6 and IL-1 with disease progression, the association was weaker than those demonstrated for TNF-alpha (Lathey, Kanangat, & Rouse, 1994; Martinez-Maza, 1992). Wesselingh et al. (1993) compared mRNA expression of various cytokines in the brains of individuals diagnosed with and without HIV-related dementia. TNF-alpha levels were higher and IL-1 and IL-4 levels were lower in individuals with dementia, whereas no differences were noted in levels of IL-6, leukemia inhibitory factor, TGF-beta, or IFN-gamma mRNA expression.

Seilhean et al. (1997) examined the association between cognitive impairment and the extent of astrocytosis and TNF-alpha expression in specific brain regions (mid-frontal cortex, subcortical and deep white matter, and basal ganglia) in 12 individuals diagnosed with AIDS (8 who were diagnosed with dementia). Both density of TNF-alpha expression and astrogliosis were positively correlated with severity of cognitive impairment.

IV. Cortisol: Alterations in the circadian rhythm cycle of adrenal hormonal levels, both elevations and suppressions, have been described in HIV-infected individuals during all disease stages (Christeff et al., 1988; Kumar, Kumar, Morgan, Szapocznik, & Eisdorfer, 1993; Membrano et al., 1987; Villette et al., 1990), though in many individuals these changes may be subtle, not exceeding clinically defined ranges (Merenich,

McDermott, Asp, Harrison, & Kidd, 1990). In a two-year longitudinal study, Findling et al. (1994) reported that relatively fewer patients showed overt cortisol abnormalities. However, a significant proportion of their sample of 53 patients (about 32%) exhibited elevations in plasma ACTH toward the end of their study, possibly reflecting the progression of subclinical adrenal dysfunction.

Relatively few studies have looked at the significance of HPA abnormalities on disease status separate from its affect on immune functioning. Lortholary et al. (1996) reported higher mean serum concentrations of cortisol in a sample of 23 men with AIDS (CDC stage IV) compared with 28 men with HIV infection that were asymptomatic or mildly symptomatic (CDC stage II and III). They also noted that CD4 T cell counts were inversely correlated with cortisol levels. Low levels of dehydroepiandrosterone (DHEA), a physiological antagonist of cortisol, have also been observed in individuals with HIV (Clerici et al., 1997b; Grinspoon & Bilezikian, 1992; Schifitto et al., 2000) and associated with advanced disease progression (Jacobsen et al., 1991; Mulder et al., 1992).

Summary

Individuals with HIV infection frequently report that the presence of somatic symptoms (especially chronic fatigue), neurocognitive impairments, and/or psychiatric difficulties adversely impacts their activities of daily living and quality of life. However, the pathogenesis of these symptoms is still poorly understood. A recent surge of research in psychoneuroimmunology has provided corroborative evidence for links between immune/HPA processes, mental status, and disease progression in various medical and psychiatric disorders. A high density of proinflammatory cytokine and cortisol receptors within the hypothalamus, medial temporal region, and frontal-subcortical systems

suggests that these neural structures may be particularly sensitive to both systemic and localized fluctuations in these molecules. These brain regions are responsible for modulating a wide variety of physiological states, collectively referred to as "illness behaviour." The physiological, neuropathological, and behavioural consequences arising from dysregulation of the immune/HPA system resembles some of the changes that accompany HIV. *In vitro* studies have yielded a better understanding of the contributions of immune and endocrine mediators to the pathogenesis of neurological insult in HIV/AIDS. However, the broader implications of these findings to the variability in clinical manifestations remains unclear. Although there continues to be a paucity of literature on the *in vivo* connections between specific mediators of biological processes and disease symptoms in HIV/AIDS, preliminary results summarized above suggest that elevated systemic concentrations of these molecules may be associated with disease progression and global measures of neurological functioning. More research is needed to determine the significance of alterations in immune and endocrine levels on *specific* neurocognitive, somatic, and depressive symptoms.

Study Objective and Predictions

This study was designed to expand upon previous research by exploring the associations between systemic indicators of immune and HPA activation, specific domains of cognitive impairment (as measured by neuropsychological test performance), fatigue, depression, and self-reported cognitive symptoms in adults with HIV/AIDS. The following main predictions are exploratory in nature, derived from the psychoneuroimmunological framework and previous research in other immune-mediated illnesses reviewed above:

(1) Elevated proinflammatory cytokines (TNF-alpha and IL-6) and higher immune activation (neopterin) will be associated with:

(a) Poorer performance on all neuropsychological domains (attention/working memory, learning efficiency, and psychomotor/processing speed)

(b) Higher levels of self-reported cognitive complaints (especially within the memory domain)

(c) Elevated depressive symptoms

(d) Increased fatigue

(2) Higher serum cortisol will be associated with:

(a) Poorer performance on measures of learning efficiency, possibly attention/working memory, but not psychomotor/processing speed

(b) Higher levels of self-reported cognitive complaints (especially within the memory domain)

(c) Elevated depressive symptoms

(d) Increased fatigue

(3) Elevated proinflammatory cytokines (TNF-alpha and IL-6), immune activation (neopterin), and cortisol levels will be associated with traditional biological indicators of disease status (i.e., lower CD4 T counts, higher CD8 T counts, and higher viral load).

Moreover, this study provides an opportunity to replicate research findings on the links between depression, fatigue, cognitive complaints, illness symptoms, and neuropsychological performance in an independent sample. The following corollary predictions were made based on recent research from the Neurobehavioural Research Unit at St. Michael's Hospital:

(4) The symptom measures (i.e., depression, fatigue, cognitive complaints, and illness symptoms) will be highly associated with each other.

(5) Of the symptom measures, only cognitive complaints will be modestly associated with neuropsychological performance. In particular, self-reported cognitive symptoms will be modestly associated with the processing speed and working memory domains.

CHAPTER II

Methodology

Participants

Forty adults with confirmed HIV infection and no past or current use of HAART medications (i.e., HAART-naïve) took part in this study[1]. Given that antiretroviral medications are intended to alter viral and immune functioning, the HAART-naïve participants were selected to reduce the possibility that the variability in biological measures may be confounded by medications or other infections accompanying disease progression. This study was approved by Research Ethics Boards at both St. Michael's Hospital (SMH) and the University of Windsor. All participants provided written informed consent prior to their involvement in the study. Recruitment was conducted through the Neurobehavioural Research Program in HIV/AIDS at SMH in Toronto, ON by contacting physicians and posting flyers at HIV specialty clinics within the region. Interested individuals were screened to exclude those with pre-existing neurological conditions (e.g., CNS opportunistic infection, seizure disorder, or head injury with loss of consciousness exceeding 30 minutes), developmental problems (e.g., diagnoses of learning disability or attention deficit disorder), lower than a Grade 6 reading level, significant medical illness (e.g., recent heart attack, kidney disease, or liver failure), history of psychotic disorder, current intravenous drug use or treatment for substance abuse, or taking medication known to significantly alter adrenocortical function (e.g., prednisone, dexamethasone, fludrocortisone acetate, or cyclophosphamide). Nine

[1] Fifty-five adults with confirmed HIV infection actually took part in this study. The HAART-naïve participants are discussed in this paper. Preliminary findings for the sample of 15 individuals on a stable HAART regimen for at least 1 ½ years (i.e., HAART-stable) can be found in Appendix A.

individuals were later removed from the analyses because they met one or more of the aforementioned exclusionary criteria.

Demographic data for the remaining sample ($N = 31$) are summarized in Table 5. The sample was comprised of 26 males (84%) and 5 females (16%). Participants were predominantly Caucasian (77%) and the majority reported sexual contact (90%) as a major risk factor for HIV infection. According to CDC disease stages classification (CDC: Centers for Disease Control and Prevention, 1992), 18 were asymptomatic (58%: CDC A1 or A2), 9 were mildly symptomatic (29%: CDC B1 or B2), and 4 had AIDS-defining illnesses or a nadir CD4 count of less than 200 (13%: CDC A3, B3, or C1-3).

The means and standard deviations for the biological indicators, symptom measures, and neuropsychological deficit scores are presented in Table 6. As a group, participants demonstrate mildly elevated symptom measures and mildly impaired neuropsychological test performance. Serum TNF-alpha and IL-6 concentrations for all individuals fell within the expected clinical reference ranges. Serum neopterin levels for 9 participants were above the clinical cut-off (i.e., > 10 nmol/L) and clinically elevated serum cortisol levels were observed in 6 participants (i.e., > 375 nmol/L).

Table 5

Demographics for HAART-naïve sample (N =31)

Variables	Mean (Standard Deviation)
Age (years)	35.6 (7.9)
Education (years)	13.4 (2.6)
WRAT reading (SS)	101.9 (9.8)
Recent CD8 Count	911.0 (287.0)
Recent CD4 Count	541.6 (322.0)
Lowest CD4 Count	429.4 (220.3)
Recent Viral Load Log	3.9 (1.0)

Table 6

Means and standard deviations of the biological indicators, symptom measures, and neuropsychological deficit scores for the HAART-naïve sample (N =31)

Variables	Mean (Standard Deviation)
TNF-alpha mRNA	1149.0 (604.4)
IL-6 mRNA	96.2 (41.6)
TNF-alpha Elisa	8.5 (1.8)
IL-6 Elisa	0.6 (0.6)
Neopterin Elisa	8.3 (4.8)
Cortisol Elisa	280.9 (100.9)
BDI Cognitive-Affective[1]	9.6 (7.0)
Piper Fatigue Total[1]	4.3 (2.1)
PAOF Total[1]	39.5 (21.1)
PAOF Memory[1]	15.1 (8.2)
Illness Total[1]	25.0 (10.7)
Total[2]	0.69 (0.6)
Processing Speed[2]	0.48 (0.7)
Working Memory/Attention[2]	0.13 (0.3)
Learning[2]	1.45 (1.3)

[1]Raw scores; [2]Composite deficit ratings
Note. BDI = Beck Depression Inventory; PAOF = Patient Assessment of Own Functioning Questionnaire

Procedure

The entire research protocol took between 2 and 2 ½ hours, with testing and the blood draw completed on the same day. Participants were briefly interviewed to gather demographic information and then asked to complete questionnaires about subjective cognitive symptoms, depressive symptoms, physical symptoms, and fatigue. A battery of neuropsychological tests was selected to assess three domains commonly affected in individuals with HIV-associated cognitive impairment: (1) attention and working memory; (2) psychomotor efficiency and processing speed; and (3) learning efficiency and memory.

Participants were asked to abstain from drinking alcohol the evening before and to avoid eating any food and drinking caffeinated or soda beverages at least 1 ½ hours before their blood samples were drawn. Blood samples were scheduled to be collected between 10 am and 5 pm (with 80% completed between 10 am and 1:30 pm) to avoid confounding the results by the natural increase in cortisol production often observed during the early morning. Blood was drawn by medical personnel in the HIV specialty clinic at SMH, and then transported for analysis to laboratories at SMH and the University of Toronto (U of T). Written permission was also obtained to access routine laboratory results from their physicians.

Measures

Demographic background. A brief interview was used to gather information about sex, age, gender, and highest level of education. Screening questions about current and past medical conditions, psychiatric history, and drug use were asked to confirm that each participant met the inclusionary criteria described above.

Disease status. Based on both CD4 T cell counts and symptomatology, the Center for Disease Control (CDC, 1992) provides a classification system for successive stages of HIV infection. Category A refers to individuals without any medical symptoms (asymptomatic) or minimally symptomatic (e.g., persistent generalized lymphadenopathy). Category B refers to symptomatic individuals with mild physical symptoms or minor opportunistic infections (e.g., oral candidiasis or herpes zoster). Category C refers to individuals who exhibit more serious infections or AIDS-defining illnesses (e.g., *Pneumocystis carinii* pneumonia, Karposi sarcoma or lymphoma, or wasting syndrome). Each of these categories is further divided into levels 1 through 3 based on nadir CD4 T cell counts: (1) $\geq$ 500 cells/mm^3; (2) 200 to 499 cells/mm^3; and (3) $<$ 200 cells/mm^3 (CDC, 1992). Individuals were classified according to CDC93 stages based on documented routine blood work results requested from the participant's physician and the presence of HIV-related or AIDS-defining illnesses obtained through self-report in the interview.

Subjective symptoms. The Patient's Assessment of Own Functioning Inventory (PAOF: Chelune et al., 1986) was used to assess subjective *cognitive* complaints. The PAOF is a self-report instrument that was "designed to elicit patients' self-perceptions regarding the adequacy of their functioning in various everyday tasks and activities" (Chelune et al., 1986, p. 96). The questionnaire can be further subdivided into memory (10 items), language and communication (9 items), sensory-perceptual and motor skills (5 items), and higher level cognitive and intellectual functions (primarily executive-type skills; 9 items) domains. Participants are instructed to rate how often they experienced a particular kind of difficulty on a 6-point scale (0= almost never; 1= very infrequently; 2=

once in a while; 3= fairly often; 4= very often; and 5= almost always). Total PAOF scores are calculated by adding the ratings on all 33 items, while domain scores are calculated by summing the ratings on the items comprising each domain. Higher scores indicate more self-reported cognitive symptoms.

The Beck Depression Inventory (BDI: Beck & Steer, 1993) was used to assess the presence and severity of *depressive* symptoms. The 21 items on this self-report questionnaire are graded on a scale from 0 to 3 to reflect increasing symptomatology. Standard clinical cut-offs for severity of depression have been defined: "minimal" (BDI < 10), "mild" (BDI 10 to 16), "moderate" (BDI 17 to 29), and "severe" (BDI >29). Items can be further subdivided to obtain cognitive-affective (sum of items 1 to 13) and somatic-vegetative (sum of items 14 to 21) scores. Unless otherwise indicated, cognitive-affective scores were used in the analyses to avoid confounding the findings with somatic items that may reflect the effects of HIV infection rather than depression. Cognitive-affective scores of 10 or less show minimal symptoms of depression (i.e., "not depressed"), while scores greater than 10 are suggestive of "moderate" depression. Of note, the findings were consistent whether total or cognitive-affective scores were used in the analyses.

The degree of *physical* symptoms was obtained through a checklist of 20 non-specific items (e.g., fever, dizziness, trouble sleeping, nausea, diarrhea, headache, skin rash, muscles aches/joint pain, weight loss, appetite reduction, and loss of sexual libido). Participants are asked to rate each item on a 5-point scale, indicating whether they have not experienced the symptom in the past month (0) or the degree to which the symptom

has bothered them over the past month (1=not at all; 2=a little; 3=a lot; 4=terribly). Higher scores reflect the presence and severity of more physical symptoms.

Fatigue was measured using the Piper Fatigue Scale-Revised (PFS-R: Piper et al., 1998). This instrument was designed and validated using a large sample of patients with cancer. The PFS-R consists of 22-items with each question rated along a 10-point scale. The total score also on a 10-point scale is obtained by summing all the items and dividing by 22. Factor analyses used in the development of the PFS-R suggest that the scale taps four dimensions: behavioural/severity (impact on activities and intensity), affective meaning (emotional attributions), sensory (energy attributions), and cognitive/mood (impact on thinking and feelings). Higher scores indicate an increased severity of fatigue and greater impact of fatigue on every day functioning.

Attention and Working Memory. Digit Span and Spatial Span, subtests of the Wechsler Memory Scale-Third Edition (Wechsler, 1997), were designed to assess auditory and visuospatial span/working memory, respectively. For Digit Span, the individual hears a series of progressively longer numbers and is required to repeat each series of numbers verbatim. Then, other number series are presented where the individual is required to provide the numbers in the reverse order. For Spatial Span, the individual is shown a board containing 9 blue-coloured blocks in a randomly spaced layout. The individual is required to copy the order of progressively longer sequences of blocks touched by the examiner, first in the same forward sequence as the examiner and then in the reverse sequence as the examiner.

Psychomotor efficiency and Processing speed. In the Symbol Digit Modalities Test (SDMT: Smith, 1982), individuals are presented with a key that contains the numbers 1 to 9 paired with different symbols. The individual is required to fill in the corresponding numbers below a series of randomly ordered symbols as quickly as possible by using the pairings in the key. The Trail Making Test and Grooved Pegboard Test (GPT: Reitan & Wolfson, 1993) are components of the Halstead-Reitan Neuropsychological Battery. Trails Part A requires the individual to connect in order a series of numbers (e.g., 1 to 2 to 3...) randomly distributed over the page. The more complex Trails Part B requires the individual to alternate between connecting a number then a letter in their corresponding order (e.g., 1 to A to 2 to B...). The Grooved Pegboard Test involves psychomotor speed and dexterity in order to fit pegs into spaces of various angles on a board. Separate scores are obtained for both the individual's dominant and non-dominant hands.

Learning efficiency and Memory. Verbal learning and memory was assessed by a word list task developed at the University of Southern California (Parker, Eaton, Whipple, Heseltine, & Bridge, 1995). The individual is orally presented with a list of 15 semantically unrelated nouns at a rate of one word every 2 seconds, and required to recall as many words as they can in any order. The individual is given three learning trials with the words presented in different orders each time. After a 30-minute delay, they are also asked to recall as many words from the list and then to provide yes/no responses as a means to determine if they can recognize the words amongst distracters. A variety of outcome measures can be obtained from the profile of responses: (1) total correct responses; (2) number of perseverations or intrusions; (3) recall consistency across the

three trials; (4) subjective organization; (5) serial position effects; (6) delayed recall; and (7) recognition hits/false positives.

The Ruff-Light Trail Learning Test (Ruff & Allen, 1999) was used to assess nonverbal learning and memory. The individual is presented with a series of interconnected circles, and instructed to draw a trail with their finger moving one circle at a time from the start to the finish. At each step, the individual receives feedback ("right" vs. "go back") by the examiner in order to assist in learning the specified 15-step trail. The first time through is random (guided by the feedback), though more steps in the trail are expected to be learned with each successive attempt. Learning efficiency is measured by examining the number of trials required to learn the trail (maximum 10) and the number of step errors made on each trial. Recall of the trail is also assessed after a 60-minute delay period.

Composite deficit ratings. Performance on the neuropsychological tests in each of the four domains was summarized into a composite clinical deficit rating based on a modified application of Heaton's Global Deficit Score (GDS). The validity of the GDS has been demonstrated in adults with HIV infection and has been described as a better measure than individual test scores, especially when investigating populations with "spotty" or subtle cognitive impairments (Carey et al., in press; Heaton et al., 1995). Individual T-scores on each of the tests were recoded according to the following 6-point scale: 0 = 40+ (normal), 1 = 35 to 39 (mild), 2 = 30 to 34 (mild to moderate), 3 = 25 to 29 (moderate), 4 = 20 to 24 (moderate to severe), and 5 = less than 20 (severe). Composite deficit ratings for each domain were calculated by summing the recoded score for all tests comprising the domain and then dividing by the total number of tests. *Attention/Working*

Memory was comprised of Digit Span and Spatial Span scores. *Processing Speed* included Trails A, Trails B, GPT dominant, GPT non-dominant, and SDMT. *Learning* was comprised of the total scores on trials 1 to 3 for the REMT and the total scores on trials 2 to completion of the RULIT. A *Total* deficit score was calculated by averaging all three of the deficit domain scores. A cut-off of 0.5 has been defined as the optimal balance between sensitivity and specificity in classifying individuals as normal versus impaired (Carey et al., in press). Higher deficit rating scores correspond with increased neuropsychological impairment.

Biological assays. Blood samples were collected in sodium citrate yellow top (8.5 ml) and serum gel separator tiger top (2 x 7ml) vacutainer tubes by trained personnel at the HIV Specialty Clinic at SMH. Due to the light-sensitive nature of neopterin, the samples were immediately covered by foil and subsequently processed and stored in dark containers. The samples were delivered, in Saf-t-pak approved containers according to GCP guidelines, to the J. Alick Little Lipid Research Laboratory at SMH, Core Laboratory at SMH, and S. Der Research Laboratory at the U of T.

I. mRNA expression: Estimates of TNF-alpha and IL-6 mRNA expression were obtained by real-time quantitative polymerase chain reactions (PCR) procedures performed at the U of T lab. Peripheral blood mononuclear cells (PBMCs) were first isolated from the blood samples using Ficoll-Hypaque gradient centrifugation. RNA was extracted from lysed PBMCs and quantified using optical density 260/280 spectrometry (Eppendorf BioPhotometer). The quality of the mRNA sample was tested for degradation by polyacrylamide capillary gel electropheresis using Agilent Bioanalyzer 2100. PCR reactions were performed in a 384-well plate format using the ABI Prism 7900HT

Sequence Detection System. cDNA was prepared by reverse transcription using 2ug of RNA according to standard procedures. Real-time PCR amplification was conducted using 10 ng of the reverse transcribed cDNA. The primers used in the procedure were designed within the U of T laboratory:

(1) HsTNFa-317/383 - AGCTGCCTTGGCTCAGACAT / GCTACATGGGAACAGCCTATTGT

(2) HsIL6-59/134 - CACTGGGCACAGAACTTATGTTG / AAAATAATTAAAATAGTGTCCTAACGCTCAT

Quantification procedures were performed in triplicate for each sample. Results represent the average estimated copies of mRNA for each participant.

II. Serum protein concentrations: The blood samples were immediately separated by centrifuge, and the plasma was aliquoted, coded, and stored at -70° until assayed. Serum concentrations of IL-6, TNF-alpha, and neopterin were obtained by trained laboratory technicians in the Lipid laboratory using commercial enzyme-linked immunosorbant assays (ELISA) kits according to manufacturer guidelines (BioSource International & IBL Hamburg). Serum cortisol concentrations were assessed by commercial radioimmunoassays in the SMH Core Laboratory according to manufacturer directions. The following normative reference ranges were provided: IL-6 (0.100 pg/ml to 10.73 pg/ml), TNF-alpha (< 20 pg/ml), neopterin (< 10 nmol/L), and cortisol (80 nmol/L to 375 nmol/L).

CHAPTER III

Results

All statistical analyses were conducted using SPSS® for windows version 10 with statistical significance defined as $p < .05$. One-tailed analyses were used because of the directionality inherent in the hypotheses. Graphical and statistical diagnostics were used to detect the presence of univariate or multivariate outliers, significant deviations from normality, nonlinearity or heteroscedasticity (Tabachnick & Fidell, 1996). One outlier (i.e., score < 3 standard deviations) was removed from the TNF-alpha mRNA analyses due to its unduly influence on the results. The neuropsychological deficit scores and some of the biological assays (TNF-alpha mRNA, IL-6 Elisa, and neopterin) were positively skewed with many individuals scores within the normal range (i.e., lower values). Transformations were not used in the analyses because the application of common transformations to these variables did not significantly alter the distribution and the interpretation of transformed measures is often unclear. Instead, results of nonparametric tests or distribution-free tests were compared to those on parametric tests. As similar patterns of findings were seen, the nonparametric results will be summarized below for continuity among analyses with any major deviations highlighted.

Performance on neuropsychological deficit indices

Most individuals performed within the mildly impaired to average ranges as determined by total and domain-specific deficit ratings (see Table 7). The working memory index had the most restricted range of performance, while learning efficiency showed the most variability. This must be taken into account when examining the meaning of subsequent analyses, whether parametric or non-parametric, as the findings may be limited by skewness and restricted range of values (Howell, 1999). The

intercorrelations between the neuropsychological deficit ratings are presented in Table 8. All domain deficit ratings were correlated with each other ($p < .05$), with the exception of the learning efficiency and working memory/attention deficit ratings.

Associations between symptom measures

Spearman correlations were calculated to examine the relations among the various symptom measures (see Table 9). Consistent with other studies, higher depression scores were moderately correlated with the endorsement of more illness symptoms ($p < .01$). Elevated depression scores were also modestly related to increased fatigue and total subjective cognitive symptoms ($p < .05$). Fatigue and self-report of cognitive symptoms were strongly correlated ($p < .001$) and illness symptoms were moderately associated with both fatigue and total cognitive complaints ($p < .01$).

Associations between the various biological indicators

Spearman correlations were calculated to explore the relations among the various biological measures (see Table 10). As predicted, the measures of proinflammatory cytokine Elisa assays (IL-6 and TNF-alpha) were positively correlated ($p < .01$). However, the mRNA expression of the proinflammatory cytokines was not associated. Contrary to expected, mRNA cytokine serum protein concentrations were not correlated with the corresponding estimated cytokine mRNA expression. Higher immune activation as estimated by elevated neopterin levels was associated with higher recent viral loads ($p < .01$) and lower recent CD4 T cell counts ($p < .05$), but not correlated with elevations in recent CD8 T cell counts ($p = .16$). Interestingly, higher serum cortisol levels were associated with lower CD4 T cell counts ($p < .05$).

Table 7

Frequencies of individuals within impairment ranges across total and domain-specific neuropsychological deficit indices within the HAART-naïve sample (N = 31)

	Total	Processing Speed	Working Memory	Learning Efficiency
Level of Impairment	n (%)	n (%)	n (%)	n (%)
Average	15 (48)	22 (71)	26 (84)	7 (23)
Mild	11 (36)	6 (19)	5 (16)	11 (36)
Mild to Moderate	5 (16)	2 (7)	0 (0)	5 (16)
Moderate	0 (0)	1 (3)	0 (0)	4 (13)
Moderate to Severe	0 (0)	0 (0)	0 (0)	3 (10)
Severe	0 (0)	0 (0)	0 (0)	1 (3)

Table 8

Spearman correlations (r_s) showing the association between the total and domain-specific neuropsychological deficit ratings within the HAART-naïve sample (N = 31)

	Total	Processing Speed	Working Memory	Learning Efficiency
Total	1.00			
Processing Speed	0.76***	1.00		
Working Memory/Attention	0.55***	0.51**	1.00	
Learning Efficiency	0.85***	0.42**	0.20	1.00

**$p < .01$ (1-tailed), ***$p < .001$ (1-tailed)

Table 9

Spearman correlations (r_s) showing the association between various symptom measures within the HAART-naïve sample (N = 31)

	Depression	Fatigue	Cognitive Total	Memory	Illness
BDI Cognitive-Affective	1.00				
Piper Fatigue Total	0.39*	1.00			
PAOF Total	0.34*	0.73***	1.00		
PAOF Memory	0.21	0.64***	0.87***	1.00	
Illness symptoms	0.52**	0.53**	0.42**	0.30	1.00

*$p < .05$ (1-tailed), **$p < .01$ (1-tailed)

Note. BDI = Beck Depression Inventory; PAOF=Patient Assessment of Own Functioning Questionnaire

Table 10

Spearman correlations (r_s) showing the association of the biological indicators within the HAART-naïve sample (N = 31)

	TNF-alpha mRNA	IL-6 mRNA	TNF-alpha Elisa	IL-6 Elisa	Neopterin Elisa	Cortisol Elisa
Recent CD8	0.08	0.20	-0.17	0.06	0.24	0.14
Recent CD4	-0.03	0.18	0.18	-0.04	-0.41*	-0.38*
Recent Viral Load	-0.16	0.05	-0.09	-0.13	0.52**	0.29
IL-6 mRNA	0.24	1.00	-----	-----	-----	-----
TNF-alpha Elisa	0.03	0.23	1.00	-----	-----	-----
IL-6 Elisa	-0.12	-0.08	0.46**	1.00	-----	-----
Neopterin Elisa	0.05	0.01	0.28	0.16	1.00	-----
Cortisol Elisa	-0.31	-0.29	-0.18	-0.03	0.16	1.00

*$p < .05$ (1-tailed), **$p < .01$ (1-tailed)

Associations between symptom measures and neuropsychological performance

The Spearman correlation coefficients for neuropsychological deficit ratings across various symptom measures are presented in Table 11. Similar to previous research, depressive symptoms and illness symptoms were not associated with neuropsychological performance. Aside from the working memory/attention deficit score, neuropsychological deficit ratings were also not associated with fatigue and cognitive complaints. Lower working memory/attention deficit scores were, however, modestly associated with higher fatigue ($p < .01$) and self-reported cognitive symptoms ($p < .05$).

Associations between biological indicators and neuropsychological performance

In order to examine the relation between biological measures and neuropsychological functioning, Spearman correlation coefficients were calculated between the neuropsychological deficit ratings, cytokine serum concentrations, cytokine mRNA expression, serum neopterin, and serum cortisol levels. Contrary to the hypothesis, no consistent pattern of associations was found between the biological indicators and neuropsychological performance (refer to Table 12).

Table 11

Spearman correlations (r_s) showing the association between various symptom measures and neuropsychological deficit scores within the HAART-naïve sample (N = 31)

	Depression	Fatigue	Cognitive Total	Memory	Illness
Total	-0.18	-0.21	-0.19	-0.17	-0.13
Processing Speed	0.03	-0.25	-0.21	-0.21	-0.01
Working Memory/Attention	-0.04	-0.37*	-0.44**	-0.36*	-0.04
Learning Efficiency	-0.30	-0.08	-0.01	0.00	-0.20

*$p < .05$ (1-tailed), **$p < .01$ (1-tailed)

Table 12

Spearman correlations (r_s) showing the association of the biological indicators and measures of depression, fatigue, illness symptoms, cognitive symptoms, and cognitive deficit indices within the HAART-naïve sample (N = 31)

	TNF-alpha mRNA	IL-6 mRNA	TNF-alpha Elisa	IL-6 Elisa	Neopterin Elisa	Cortisol Elisa
BDI Cog-Aff[1]	0.12	0.40*	0.13	0.18	0.28	-0.04
Piper Fatigue Total[1]	-0.13	0.38*	0.04	0.13	0.07	-0.05
PAOF Total[1]	0.00	0.21	-0.12	-0.16	0.15	-0.19
PAOF Memory[1]	0.02	0.28	-0.16	-0.35*	0.16	-0.10
Illness Total[1]	-0.23	0.16	-0.19	0.24	0.06	0.06
Total[2]	0.18	-0.04	-0.12	0.00	0.11	-0.23
Processing Speed[2]	0.18	-0.06	-0.06	0.08	0.02	-0.23
WM/Attn[2]	-0.02	-0.06	-0.32*	-0.11	-0.17	-0.06
Learning[2]	0.07	0.01	-0.14	-0.10	0.20	-0.12

[1]Raw scores; [2]Composite deficit ratings
*p < .05 (1-tailed), **p< .01 (1-tailed)
Note. BDI Cog-Aff = Beck Depression Inventory Cognitive-Affective score; PAOF = Patient Assessment of Own Functioning Questionnaire; WM/Attn = Working Memory and Attention

Associations between biological indicators and symptom measures

Spearman correlations between the six biological measures, depressive symptoms (BDI cognitive-affective), fatigue (PFS-R total scores), subjective cognitive symptoms (PAOF total and memory scores), and total illness symptoms (HIV symptom checklist) are summarized in Table 12. As predicted from the literature, higher depressive symptoms were modestly associated with elevated IL-6 mRNA expression ($p < .05$). Modest positive correlations were also noted for IL-6 mRNA expression and fatigue ($p < .05$). A similar pattern of findings was obtained with the Pearson product-moment correlations, though the associations between the biological indicators and symptom measures were stronger. This may partly reflect the fact that nonparametric tests have lower power relative to the corresponding parametric test (Howell, 1999). The Pearson correlational analyses showed that IL-6 mRNA expression was correlated with all symptom measures, including depression ($r = 0.50, p < .01$), fatigue ($r = 0.33, p < .05$), total cognitive complaints ($r = 0.32, p < .05$), memory complaints ($r = 0.37, p < .05$), and illness symptoms ($r = 0.34, p < .05$). Higher serum neopterin was also associated with elevated depressive symptoms ($r = 0.33, p < .05$).

Given the high intercorrelations between symptom measures, partial correlations were used to further tease apart the relations with IL-6 mRNA expression. When the influence of depression was controlled, IL-6 mRNA expression was no longer correlated with fatigue ($pr = 0.19, p = .174$), illness symptoms ($pr = 0.10, p = .31$), total cognitive complaints ($pr = 0.18, p = .19$), or memory complaints ($pr = 0.27, p = .08$). Inversely, the association between depression and IL-6 mRNA expression weakened but remained statistically significant after removing the influences of fatigue, total cognitive complaints, and illness symptoms ($pr = 0.39, p < .05$).

Associations between severity of depression and IL-6 mRNA and neopterin levels

Individuals were grouped according to the severity of their depression in order to clarify the relation between depressive symptoms, IL-6 mRNA expression, and serum neopterin levels. In order to capture the range of severity, groups were defined according to standard clinical cut-offs on the total BDI score (Beck & Steer, 1993): "minimal" (BDI < 10), "mild" (BDI 10 to 16), "moderate" (BDI 17 to 29), and "severe" (BDI >29). Participants' concentrations of IL-6 mRNA and neopterin divided across the four levels of depression are shown in Figures 3 and 4. Although the small number of individuals in each group limits the generalizability of these findings, some interesting patterns can be seen. All of the severely depressed individuals showed high IL-6 mRNA expression (i.e., above 125 copies/10ng of c-DNA) and high neopterin levels (i.e., close to or above the clinical cut-off of 10 nmol/L).

One-way ANOVAs verified that differences existed between depression severity subgroups for both IL-6 mRNA expression [$F(3, 24) = 7.72$, $p < .001$] and serum neopterin concentrations [$F(3, 26) = 3.39$, $p < .05$]. Pairwise multiple comparisons were completed to specifically determine which of the groups' means differed from each other. The Bonferroni method, which assumes equal variances (supported by non-significant Levene statistics), was selected to adjust for inflation of Type I error rate with multiple comparisons. The severely depressed individuals had higher mean IL-6 mRNA expression compared with the means for the moderate ($p < .01$), mild ($p < .01$), and minimally ($p < .001$) depressed groups (see Figure 5). The severely depressed individuals had higher mean serum neopterin levels compared with the means for mild ($p < .05$) and minimally ($p < .05$) depressed groups, but was not different from the mean of the moderately depressed group (see Figure 6).

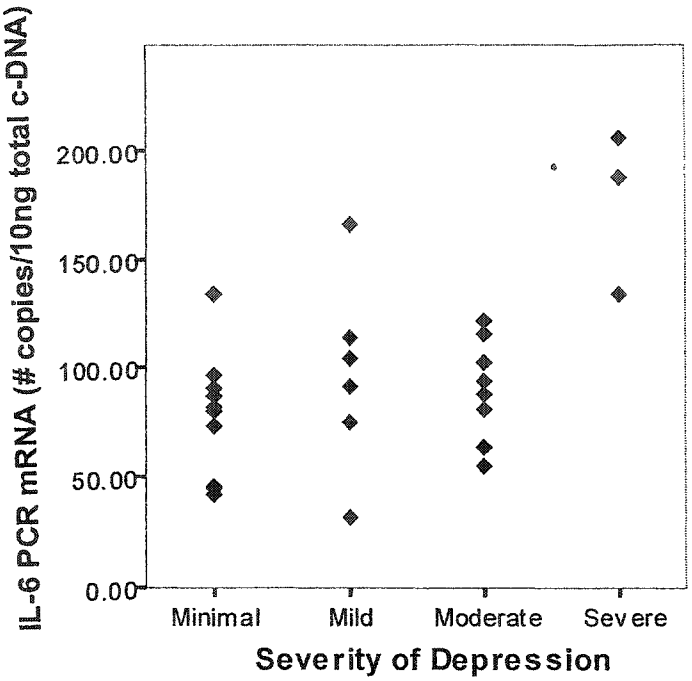

Figure 3. Scatterplot showing IL-6 mRNA expression for individual participants divided according to the severity of their depressive symptoms.

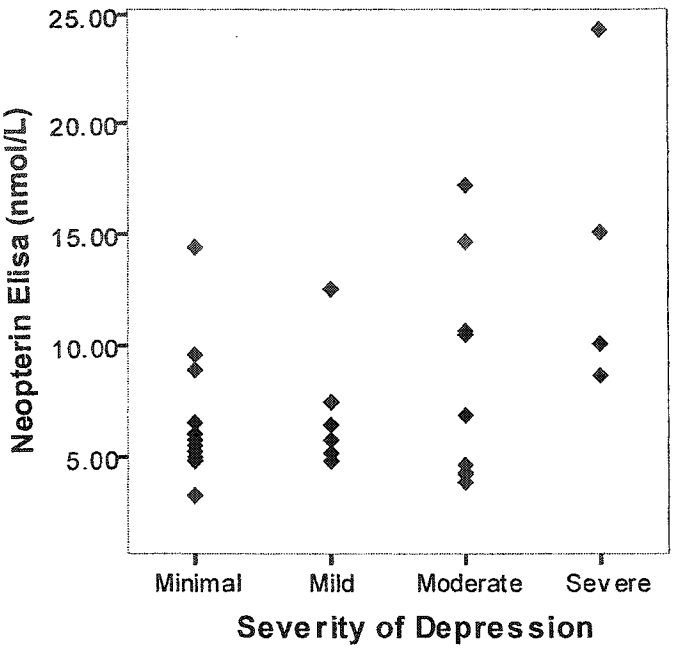

Figure 4. Scatterplot showing serum neopterin concentrations for individual participants divided according to the severity of their depressive symptoms.

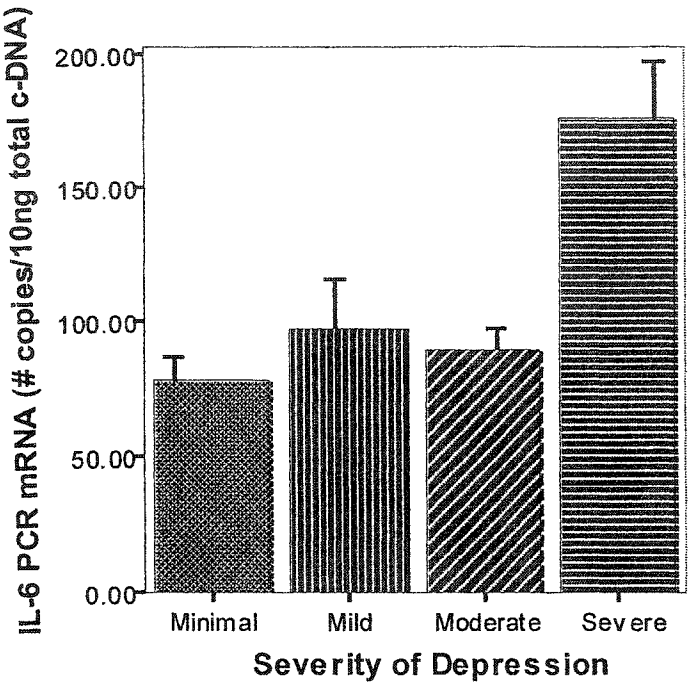

Figure 5. Mean IL-6 mRNA expression as a function of depression severity.

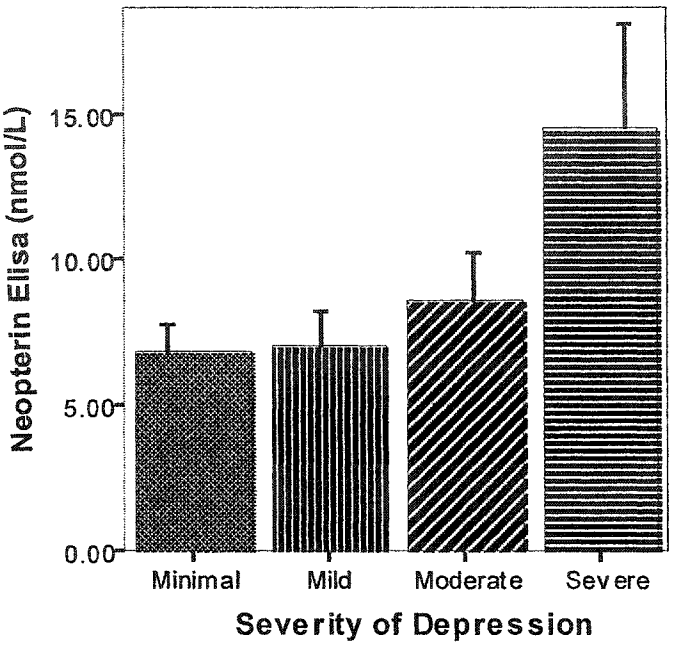

Figure 6. Mean serum neopterin concentrations as a function of depression severity.

Potential confounding influences on the biological measures

Interactions with antidepressant medications. The influence of antidepressants on the association between IL-6 mRNA expression, serum neopterin, and depression was explored by grouping participants into those currently using antidepressants (n = 18) and those not taking any antidepressants (n = 13). All types of antidepressants (e.g., tricyclics and selective serotonin reuptake inhibitors) were considered together given the small sample size. Means and standard deviations for age, education, estimated reading level, blood indicators, biological measures, and symptom measures for the separate antidepressant groups are provided in Table 13. No differences were evident between the individuals taking and not taking antidepressants on the demographic variables, with the exception of the mean age for the antidepressant group being slightly higher than the mean age of those not taking any antidepressants [F (1, 29) = 4.33, p < .05]. Mean biological indicators and symptom measures were not different for participants taking versus not taking antidepressants.

Given the reduced power associated with nonparametric tests and the small sample sizes, both Pearson (r) and Spearman (r_s) correlations between depressive symptoms (BDI cognitive-affective scores), IL-6 mRNA expression, and serum neopterin levels are separately calculated for the antidepressant groups. Depressive symptoms and IL-6 mRNA expression remained modestly associated for both the antidepressant (r_s = 0.32, p = .14; r = 0.60, p < .05) and no antidepressant groups (r_s = 0.45, p < .05; r = 0.39, p = .08). On the other hand, an interesting interaction was observed for neopterin serum concentrations and depressive symptoms across antidepressant groups. Although neopterin and depressive symptoms were strongly associated in the antidepressant group

(r_s = 0.83, p < .001; r = 0.78, p < .001), the association was nullified in the group not taking any antidepressants (r_s = -0.25, p > .05; r = -0.08, p > .05). These findings are graphically illustrated by the scatterplot in Figure 7.

In order to further investigate the nature of this interaction, individuals were divided into not depressed and depressed groups based on a BDI cognitive-affective cut-off score of 10 (Beck & Steer, 1993). Participants' concentrations of IL-6 mRNA and neopterin for depressed versus non-depressed individuals are separately shown by antidepressant groups in Figures 8 and 9. Despite the small number of individuals in each group, some interesting patterns are evident. For individuals taking antidepressants, variability in IL-6 mRNA expression was apparent for both depressed and not depressed individuals. Although variability was also apparent among individuals not taking antidepressants, a greater proportion of depressed as compared with non-depressed individuals had higher levels of IL-6 mRNA expression. Depressed individuals taking antidepressants showed relatively higher neopterin serum concentrations in comparison with non-depressed individuals taking antidepressants. In fact, all six depressed individuals on antidepressants were above the clinical reference range for neopterin (i.e., cut-off >10 nmol/L) while all seven non-depressed individuals on antidepressants were within normal expectations. More variability was seen among both the depressed and non-depressed individuals not on antidepressants, though the majority (80%) of individuals not taking antidepressants had serum neopterin levels within normal limits.

ANOVAs separately performed by antidepressant group provided further support for an interaction between depression, antidepressants, and neopterin levels. Although mean neopterin levels of the depressed and non-depressed groups were not different for

those not taking antidepressants [$F(1, 15) = 0.00, p > .05$], mean neopterin levels were higher in the depressed as compared to non-depressed group for those taking antidepressants [$F(1, 11) = 45.66, p < .001$] (see Figure 10).

Table 13

Demographic data, biological indicators, and symptom measures for HAART-naïve individuals on (n = 13) and not on antidepressants (n = 18)

	Mean (Standard Deviation)	
Variables	Antidepressants (n= 13)	No Antidepressants (n= 18)
Age (years)*	38.8 (9.0)	33.2 (6.3)
Education (years)	13.3 (2.6)	13.5 (2.6)
WRAT reading (SS)	101.9 (9.6)	101.9 (10.3)
Recent CD8 Count	941.4 (331.0)	873.8 (236.3)
Recent CD4 Count	593.5 (360.5)	499.4 (292.2)
Lowest CD4 Count	453.6 (248.2)	412.4 (204.5)
Recent Viral Load Log	4.0 (0.9)	3.7 (1.0)
TNF-alpha mRNA	961.8 (373.3)	1298.7 (717.5)
IL-6 mRNA	103.7 (48.8)	89.7 (34.7)
TNF-alpha Elisa	8.8 (1.0)	8.2 (2.2)
IL-6 Elisa	0.7 (0.5)	0.6 (0.8)
Neopterin Elisa	8.8 (4.6)	7.9 (5.0)
Cortisol Elisa	265.8 (87.8)	292.5 (111.1)
BDI Cognitive-Affective	9.2 (8.2)	9.9 (6.1)
Piper Fatigue Total	4.6 (1.1)	4.0 (2.7)
PAOF Total	39.9 (18.7)	39.2 (23.3)
PAOF Memory	15.0 (8.0)	15.1 (8.7)
Illness Total	23.2 (9.8)	26.4 (11.4)

* $p < .05$ (Means differ for two groups)

Note. BDI= Beck Depression Inventory; PAOF = Patient Assessment of Own Functioning Questionnaire

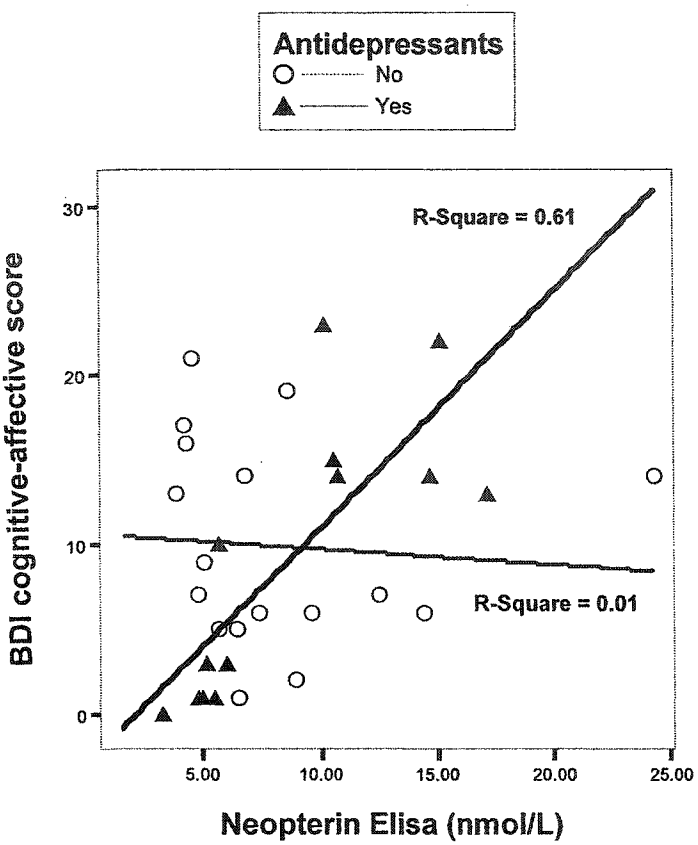

Figure 7. Scatterplot showing the relations between depressive symptoms and serum neopterin levels separated by antidepressant groups.

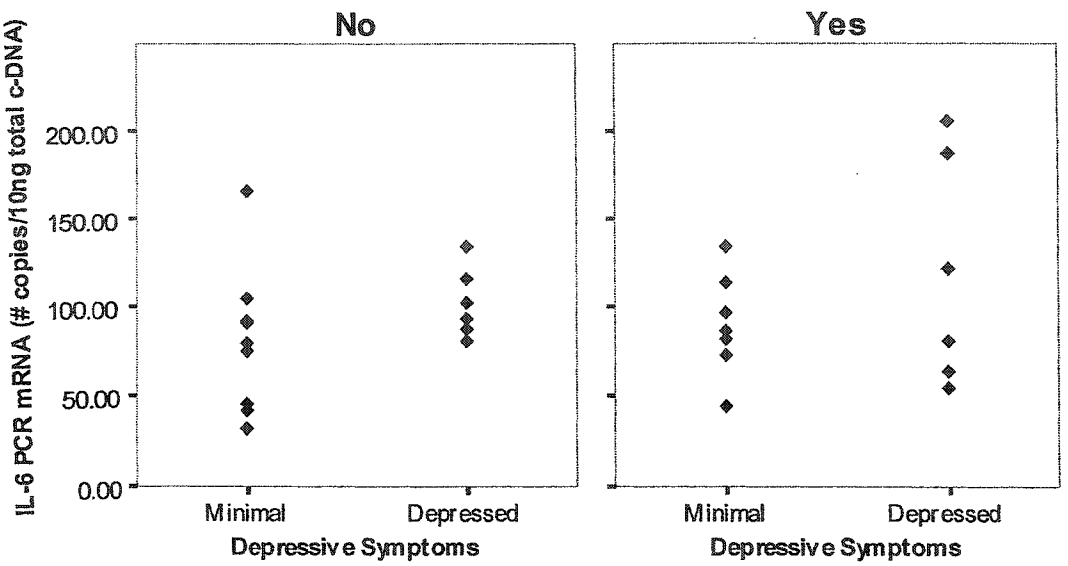

Figure 8. Scatterplots showing the relations between depressive symptoms and IL-6 mRNA expression separated by antidepressant groups.

Note. No = individuals not taking any antidepressant medication, Yes = individuals taking antidepressants

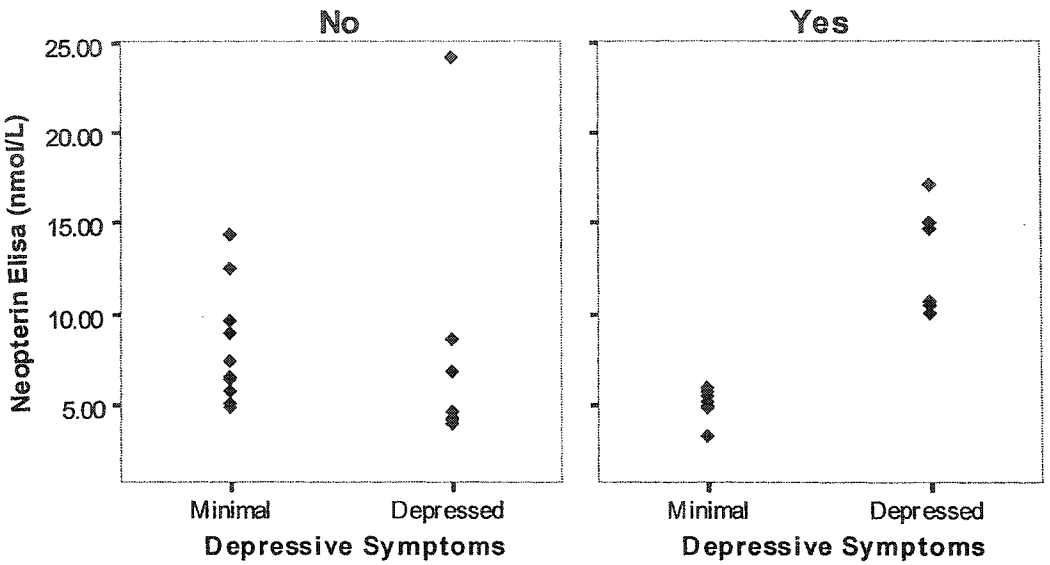

Figure 9. Scatterplots showing the relations between depressive symptoms and serum neopterin levels separated by antidepressant groups.

Note. No = individuals not taking any antidepressant medication, Yes = individuals taking antidepressants

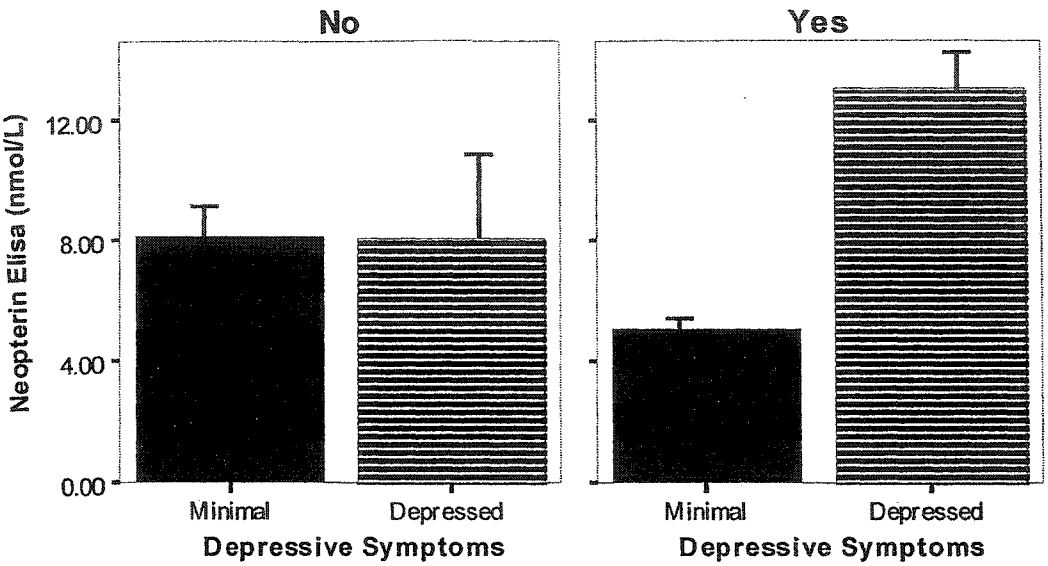

Figure 10. Mean serum neopterin concentrations for depressed and non-depressed individuals separated by antidepressant groups.

Note. No = individuals not taking any antidepressant medication, Yes = individuals taking antidepressants

Sex. Differences in production and cyclic regulation of hormones between the sexes could potentially influence the biological measures. In particular, cortisol levels can be suppressed by the presence of other hormones which considerably vary over the month in females. Although there are too few female participants to analyse sex as separate groups, the association between biological assays and symptom measures was examined with the 5 female participants removed from the sample. Taking into consideration the reduction in power due to fewer participants overall, the pattern of results essentially remains unchanged. IL-6 mRNA expression was correlated with all the symptom measures: BDI cognitive-affective (r_s = 0.54, $p < .01$; r = 0.57, $p < .01$), Piper Fatigue Scale (r_s = 0.51, $p < .01$; r = 0.44, $p < .05$), PAOF total (r_s = 0.38, $p < .05$; r = 0.39, $p < .05$), PAOF memory (r_s = 0.43, $p < .05$, r = 0.42, $p < .05$), and to a lesser extent with HIV symptom checklist (r_s = 0.29, p = .09; r = 0.43, $p < .05$). A more modest association was present between serum neopterin levels and depressive symptoms (r_s = 0.26, p = .1; r = 0.37, $p < .05$), though neopterin and depressive symptoms remained strongly correlated in the group of individuals taking antidepressants (r_s = 0.80, $p < .001$; r = 0.75, $p < .01$). The correlation coefficients for the other biological indicators (including serum cortisol) with symptom measures and neuropsychological deficit ratings were non-significant.

Disease stage. Severity of disease progression could also potentially impact the biological measures. Although the majority of individuals in the HAART-naïve group were asymptomatic (n = 18, 58%) or mildly symptomatic (n = 9, 29%) as defined by CDC93 staging criteria, 4 individuals had AIDS-defining illnesses or a nadir CD4 count of less than 200. The correlational analyses were rerun without the four individuals at

advanced stages. IL-6 mRNA expression remained associated with scores on the BDI cognitive-affective ($r_s = 0.45, p < .01$; $r = 0.53, p < .01$) and to a lesser degree with the Piper Fatigue Scale ($r_s = 0.40, p < .05$; $r = 0.39, p < .05$), PAOF total ($r_s = 0.24, p = .13$; $r = 0.34, p = .05$), PAOF memory ($r_s = 0.28, p = .09$; $r = 0.37, p < .05$), and HIV symptom checklist ($r_s = .19, p = .18$; $r = 0.36, p < .05$). In contrast, the association between serum neopterin and BDI cognitive-affective scores was weakened and no longer statistically significant ($r_s = 0.20, p = .16$; $r = 0.27, p = .09$) when the participants with AIDS were removed. This may stem, in part, from the reduced sample size, decreased variability in neopterin values, as well as the influence of the AIDS individuals, as three out of the four participants with AIDS had elevated serum neopterin levels outside the normal reference range (see Figure 11). However, the association between neopterin and depressive symptoms remained strongly correlated in the group of individuals taking antidepressants ($r_s = 0.88, p < .001$; $r = 0.84, p < .001$).

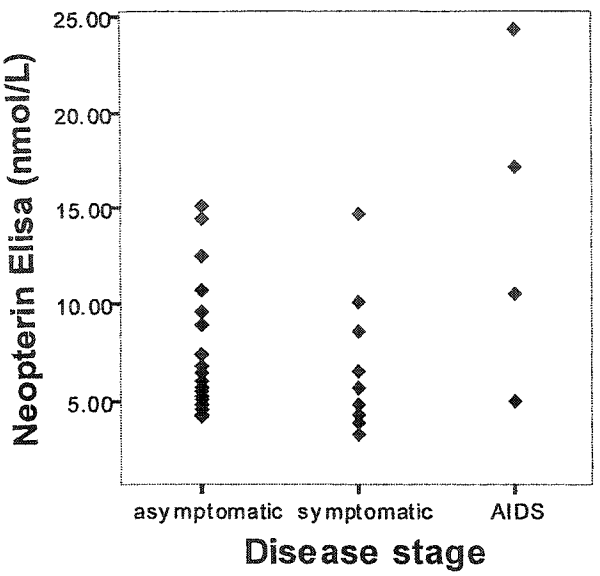

Figure 11. Scatterplot showing serum neopterin levels across disease stage.

CHAPTER IV

Discussion

Traditionally, neuropsychology has been concerned with explaining human behaviour in terms of central nervous system (CNS) functioning (i.e., defining brain-behaviour relationships). Recent work in the field of psychoneuroimmunology provides mounting support for integral connections between systemic biological processes (immune and endocrine) and key brain systems responsible for governing a wide variety of physiological and behavioural responses including affect and cognition. Transient elevations in biological mediators (cytokines and hormones) are pivotal for instigating physiological responses that permit adaptation to environmental changes including physical (e.g., acute infection) and psychological stressors (e.g., perceived threats). "Illness or sickness behaviours" consequently arise as the body redistributes resources and actively fights acute infections: fever, malaise, fatigue, depressed mood, decreased appetite, accelerated weight loss, increased need for sleep, reduced sex drive, increased sensitivity to pain, and reduced cognitive efficiency. While adaptive in the short-term, chronic dysregulation of biological processes and associated prolongation of "illness behaviours" could significantly impede an individual's ability to function in everyday life.

"Illness behaviours" resemble the somatic, affective, and cognitive symptoms often accompanying various medical conditions, including those frequently present in individuals with HIV/AIDS. As a result of remarkable advancements in antiretroviral drug therapies over the past 20 years, many individuals are now living and coping with HIV as a chronic illness. Although medications have effectively slowed disease

progression, symptoms of chronic fatigue, depression, and cognitive difficulties remain prevalent and often adversely impact quality of life. Management of these clinical symptoms can be challenging given the complexity of potential factors (both biological and psychological) that may underlie the differential expression across individuals. While immune and endocrine dysfunction in HIV has been well-described at a cellular pathophysiological level, there remains a paucity of literature examining the possible links between these biological alterations and the development of specific clinical symptoms.

This pilot study aimed to integrate biological studies on the neuropathogenesis of HIV within a broader clinical context by exploring the associations of systemic indicators of immune system (neopterin, IL-6, and TNF-alpha) and HPA axis (cortisol) activation with the presence and severity of the following clinical symptoms in a sample of 31 HAART-naïve participants with HIV infection: (1) specific domains of cognitive impairments as measured by performance on neuropsychological tests (attention/working memory, learning efficiency, and psychomotor/processing speed); (2) self-reported cognitive symptoms; (3) a subjective measure of fatigue; and (4) self-reported depressive symptoms.

Evaluation of Predictions and Study Limitations

Hypothesis 1. The first prediction was only partially supported in this pilot investigation. While immune markers were not correlated with objective measures of cognitive impairment in the present study (Hypothesis 1a), associations were obtained between some immune markers and subjective symptom measures (Hypotheses 1b to d).

I. Symptom measures: Elevated immune activation (as measured by serum neopterin levels and mRNA expression of the proinflammatory cytokine IL-6) was associated with depressive symptoms. Higher serum IL-6 mRNA expression was also modestly associated with elevated fatigue, total and memory cognitive complaints, and illness symptoms, though only the relation with depression remained significant after the overlapping influences of the other symptom measures were removed. More specifically, both the *presence and severity* of depressive symptoms were related to elevated immune activation, such that the most severely depressed individuals in this sample showed higher levels of IL-6 mRNA expression and neopterin concentrations. Similarly, several recent investigations have shown links between depression and immune activation, as measured by both elevated serum IL-6 and neopterin in depressed individuals (e.g., Bonaccorso et al., 1998; Musselman et al., 2001; Schlatter et al., 2004; Trzonkowski et al., 2004; Zautra et al., 2004). In general, studies comparing patients diagnosed with Major Depressive Disorder (with or without comorbid medical conditions) versus non-depressed individuals have found group differences in mean levels of serum immune measures, whereas relatively fewer studies have found an association between biological measures and the severity of depression (see Table 3). While condition/control group differences are initially useful in identifying measures of interest to study, they provide limited information about the individual variability in symptom expression within a medical condition. More in-depth exploration of factors within a specific condition is necessary for identifying subgroups and associated characteristics that may place particular individuals at higher risk for the development of certain clinical symptoms.

In the present study, the effects of antidepressant medication on the link between immune activation and depressive symptoms was explored. Although no association was evident in the individuals not taking antidepressants, neopterin and depressive symptoms were strongly associated in the group of individuals currently taking antidepressants. In the antidepressant group, some of the individuals showed both reduced depressive symptoms and lower neopterin levels, suggesting that the antidepressant medications were effective. In contrast, a subsample of individuals on antidepressants continued to endorse high levels of depressive symptoms and had elevated neopterin levels. This subsample may represent individuals not responding to the treatment similar to previously described treatment-resistant groups (Kubera et al., 2004; Lanquillon et al., 2000). Both Xia et al. (1996) and Maes et al. (1999) have demonstrated immunosuppressive effects of antidepressants *in vitro* using serum from healthy adults. In contrast, most *in vivo* studies have failed to show significant changes in immune markers with short-term (< 3 months) antidepressant treatment in inpatient or acutely depressed samples (see Table 4). Many individuals require long-term treatment with antidepressants to achieve desired prolonged effects. Although data on the duration of antidepressant treatment was not systematically collected in the present study, the available information suggests that many individuals in the present sample had been taking the antidepressants much longer than 3 months. Moreover, *mean change scores* used in previous investigations may obscure individual differences in biological markers, whereas the consideration of each individuals' post-treatment levels relative to standard clinical cut-offs in the present study permitted the isolation of subsamples within the antidepressant group (see Figure 9). Similarly, when Lanquillon et al. (2000) examined treatment

responders and non-responders separately, a decline in some immune markers was apparent but *only* for the individuals who were responding to the antidepressant at 6 weeks.

II. Cognitive impairment. Contrary to expected, no consistent pattern of association was found between the biological indicators and neuropsychological performance across total, attention/working memory, learning efficiency and memory, and psychomotor/processing speed deficit ratings in the present sample. Several potential explanations may be offered for the absence of this association. Although the HIV virus has been shown to enter the CNS within days to weeks of infection (e.g. Davis et al., 1993; Resnick et al., 1988), cognitive impairments are rarely evident at diagnosis and increase in prevalence with duration of the illness and advancing disease stage (Bornstein et al., 1993; White et al., 1995). Research on the cellular mechanisms underlying neurotoxicity suggest that the HIV virus does not directly infect neurons but instead is stored and transported to the brain via macrophages. The release of viral and cellular toxins (e.g., proinflammatory cytokines or oxygen radicals) from chronic low-grade activation of macrophages is thought to indirectly damage the CNS (e.g., Gendelman et al., 1994; Minagar et al., 2002). Given the complexity and resilience of the brain, multiple insults exacerbated by transient states of heightened immune activation (that also perpetuate phases of more intense viral replication) may be required prior to showing significant cognitive impairments as measured by below expected performance on neuropsychological tests. As such, measurement of an individual's biological status at a single time-frame may not accurately correlate with the damage already done to the CNS. While transient fluctuations in proinflammatory cytokines and immune activation may

contribute to the mild, intermittent cognitive inefficiency experienced in every day life, a single session of objective neuropsychological tests may not capture these subtle subjective cognitive changes as individuals may be able to compensate within the testing session. Neuropsychological testing provides an estimate of the individual's best cognitive performance within an isolated and time-limited context. However, this performance may be unrepresentative of the ongoing demands faced in everyday situations especially in individuals with relatively mild changes in their cognitive abilities. On the other hand, more stable or chronic elevations in biological indicators of immune activation may accompany further deterioration of immune system functioning at advanced disease stages (e.g., Aukrust et al., 1994; Baier-Bitterlich et al., 1996; Kulinkovich et al., 1992). This may account for why a few studies have found associations between elevated immune activation (in particular neopterin and TNF-alpha) and more frank neurological impairment or dementia (Ryan et al., 2002; Seilhean et al., 1997), HIV encephalopathy (Grimaldi et al., 1991), as well as the presence of neurological diseases, such as meningitis, CNS opportunistic infections, and inflammatory demyelinating polyneuropathies (Griffin et al., 1991; Wesselingh et al., 1994) in patients diagnosed with AIDS.

Another possibility could be that a more modest association was obscured due to the size and characteristics of the present sample. While the sample size is adequate to detect a moderate or strong correlation, a much larger sample size ($N > 150$) may be needed to detect a more modest association (Howell, 1999). Although some preliminary studies (e.g., Kirschbaum et al., 1996; Kozora et al., 2001; Reichenberg et al., 2001; Spath-Schwalbe et al., 1998) with similar sample sizes have obtained modest correlations

between biological indicators and cognitive impairments in other medical conditions or in healthy individuals under experimental manipulations (see Table 2), larger samples of adults with HIV infection may be needed given the demographic and clinical variability in this population. For example, other studies have required large sample sizes in order to capture small but clinically significant relations between neuropsychological performance and subjective cognitive complaints in samples of adults with HIV infection (e.g., Carter et al., 2003; Rourke et al., 1999a).

In addition to suppressing viral replication, initiation of antiretroviral medications may be accompanied by reductions in biological indicators of immune activation such as neopterin (e.g., Amirayan-Chevillard et al., 2000; Zangerele et al., 2002). Opportunistic infections, more frequently present with advanced disease progression, may alter immune status and cytokine profiles (e.g., Valdez et al., 1997-1998). HAART-naïve participants were specifically selected to reduce these potential confounds. Physicians typically initiate HAART treatment when CD4 T cell counts significantly drop (often below 200) and symptoms ensue. Hence, the majority of the HAART-naïve sample were asymptomatic (58%) and mildly symptomatic (21%) according to CDC disease stage classification criteria (CDC, 1992). Hence, the manifestation of clinical symptoms in the present sample may have been reduced by this selection bias. The restricted variability in neuropsychological test performance and biological measures (i.e., most scores within normal limits) may have contributed to the limited findings.

Hypothesis 2. Higher serum cortisol was not associated with poorer performance on the neuropsychological measures, higher self-reported cognitive complaints, elevated depressive symptoms, nor increased fatigue in the present sample. These findings are

contrary to previous studies (cited in Tables 1, 2, and 3) showing associations between elevated cortisol and higher fatigue, depressive symptoms, and impaired cognitive function. The link between elevated cortisol and impaired cognitive function (in particular on measures of verbal declarative memory) has been consistently demonstrated using experimental manipulations (corticosteroid administration or exposure to psychosocial stressor) in healthy participants (e.g., Kirschbaum et al., 1996; Newcomer et al., 1999). Higher cortisol levels have also been associated with cognitive impairment, depression, or fatigue in medical conditions that have *significant* alterations in adrenal functioning due to the disease process itself (e.g., Cushing's syndrome, early withdrawal of alcoholics, or Alzheimer's disease), treatment with corticosteroids (e.g., rheumatoid arthritis), or under conditions of dexamethasone suppression (e.g., Major Depressive Disorder) (e.g., Errico et al., 2002; Keenan et al., 1995; Mauri et al., 1993; Starkman et al., 1992; Van Loden et al., 1998; Umegaki et al., 2000; Weiner et al., 1997; Wolkowitz et al., 1990). While alterations in the circadian rhythm cycle of adrenal hormonal levels have been documented in some individuals with HIV infection (e.g., Christeff et al., 1988; Kumar et al., 1993; Villette et al., 1990), most studies have failed to find *overt* HPA abnormalities in the vast majority of individuals with HIV especially in individuals at early disease stages (e.g., Findling et al., 1994; Merenich et al., 1990). The association between higher serum cortisol levels and advanced disease progression (Findling et al., 1994; Lortholary et al., 1996) may reflect dysregulation from mounting stressors and/or direct pathological consequences of the HIV virus or opportunistic infections on the endocrine/immune negative regulatory mechanism (refer to Figure 2). In the present sample, the estimated serum cortisol levels taken at a single time-point in the late

morning to early afternoon fell within normal limits for most individuals (81%). Inclusion of more participants at advanced disease stages may increase the variability of cortisol levels within the sample. The potential subclinical dysregulation of the HPA axis in HIV infection may be better captured by measuring cortisol over the entire 24 hour cycle, as alterations may be more apparent at peak times early in the morning or trough times in the late evening. Given the broadly defined normal range of cortisol levels, measurement of disproportionate responses following experimental manipulations of the HPA axis (e.g., dexamethasone suppression, challenge with lipopolysaccharide, or presentation with psychological stressors) may provide a more effective means to examine individual alterations and their association with clinical symptoms in individuals with HIV infection.

Hypothesis 3. Contrary to previous investigations (e.g., Aukrust et al., 1994; Godfried et al., 1994; Kulinkovich et al., 1992), the serum and mRNA expression of proinflammatory cytokines were not directly associated with traditional biological indicators of disease status (i.e., lower CD4 T counts, higher CD8 T counts, and higher viral load). Given the possibility of more transient alterations in proinflammatory cytokine levels at early disease stages, single measures of biological indicators may be insufficient for tracking corresponding changes in immune functioning. The inflammatory cytokine cascades observed in typical immune responses to infection (Janeway & Travers, 1997) suggests that increased cytokine production may not directly accompany but, in fact, precede resultant immune cell alterations (e.g., cytokines trigger macrophage and CD4 T cell recruitment and stimulation, which may, in turn, enhance viral infection of immune cells and subsequent viral replication). Associations apparent in

studies of individuals across disease stages may reflect the chronic elevations in proinflammatory cytokines with more advanced disease progression (Aukrust et al., 1994; Godfried et al., 1994; Kulinkovich et al., 1992). Longitudinal studies sampling biological indicators across multiple time points may provide a means to further elucidate the exact nature of the relation between proinflammatory cytokines and disease progression in HIV.

On the other hand, reservoirs of the HIV virus contained within macrophages are thought to instigate the chronic low-grade activation and release of toxins from the host macrophage (Gendelman et al., 1994; Minagar et al., 2002). Hence serum neopterin levels, a general marker of macrophage activation and the extent of oxidative stress within the immune system, may be more directly correlated with recent measures of immune cell functioning (CD4 and CD8 cells) and viral replication (viral load). In the present study, elevated serum neopterin levels were associated with some of the traditional markers of disease progression (i.e., higher recent viral loads and lower recent CD4 T cell counts, but not correlated with elevations in recent CD8 T cell counts). This finding is consistent with a few previous investigations documenting elevated neopterin levels in many individuals at early disease stages and showing subsequent increases in neopterin levels with advanced disease status (e.g., Baier-Bitterlich et al., 1996; Fahey et al., 1990; Metha et al., 1996).

Interestingly, higher serum cortisol levels were also associated with lower CD4 T cell counts in the present sample. Lortholary and colleagues (1996) reported a similar finding in a study comparing cortisol levels in individuals across disease stages. Elevated cortisol levels may hasten progression of HIV infection by altering cellular metabolism

(Brooke and Sapolsky, 2000) or by suppressing cell-mediated immunity and the production of Type 1 cytokines such as IL-2, IL-12, and IFN-gamma (Clerici et al., 1997; Rook et al., 1993; Sapse, 1997). A shift toward humoral immunity and elevated type 2 cytokines (IL-4 and IL-10) may trigger destruction of CD4 T cells, reduce the efficacy of cytotoxic mechanisms at eliminating HIV-infected cells, and/or initiate a less effective means (i.e., antibody neutralization) to manage the HIV virus. This imbalance in type 1 and type 2 expression has frequently been described in individuals with HIV infection especially at advanced disease stages (Clerici et al., 1997b; Fauci, 1996; Klein et al., 1997; Salvaggio, Balotta, Galli, & Clerici, 1995) and has been associated with reduction in CD4 T cell counts, time to AIDS diagnosis, and time to death (Dolan et al., 1995; Lucey et al., 1991).

Hypotheses 4 and 5. This study also provided an opportunity to replicate research findings on the links between depression, fatigue, cognitive complaints, illness symptoms, and neuropsychological performance in an independent sample. Consistent with other studies, elevated depression scores were associated with increased fatigue (Millikin et al., 2003), endorsement of more illness symptoms (Carter et al., 2003), and higher subjective cognitive symptoms (e.g., Bassel et al. 2002; Beason-Hazen et al., 1994; Hinkin et al., 1996; Moore et al., 1997; Rourke et al., 1999a). Total subjective cognitive complaints were also associated with fatigue (Millikin et al., 2003) and illness symptoms (Carter et al., 2003). While symptom measures were expected to be highly intercorrelated, neuropsychological performance was not expected to be associated with subjective symptoms of depression, fatigue, or medical illnesses based on previous null findings in large samples of individuals with HIV/AIDS (e.g., Carter et al., 2003; Millikin

et al., 2003). Some selective studies have shown poorer performance in depressed patients as compared with normal controls on tests of attention (e.g., Landro, Stiles,& Sletvold, 2001; Williams et al., 2000), processing speed (e.g., Basso, Lowery, Neel, Purdie, & Bornstein), verbal recall (e.g., Fossati, Deweer, Raoux, & Allilaire, 1995; Ilsley, Moffoot, and O'Carroll, 1995), verbal fluency (e.g., Landro et al., 2001), and executive functioning (e.g., Ilonen et al., 2000). However, recent meta-analyses have challenged the conventional notion that neuropsychological deficits accompany major depression. When stringent methodological designs and only individuals with unipolar depression (i.e., no evidence of mania or psychoses) were considered, the analyses failed to provide support for consistent and substantial differences between depressed groups and normal controls (e.g., Burt, Zembar, & Niederehe, 1995; Veiel, 1997). Ahmad (2004) used rigorous cluster analytic techniques to further demonstrate that neither depressed children nor adults were differentiated from controls in terms of their pattern of performance on a comprehensive neuropsychological test battery. Similarly, neuropsychological performance was not related to symptoms of depression, fatigue, or medical illnesses in the present sample.

As previously mentioned, self-reported cognitive symptoms and neuropsychological test performance sometimes do not directly correspond with each other in clinical practice. Some studies in samples of individuals with HIV infection have failed to find any association between subjective measures of cognitive difficulties in everyday situations and neuropsychological test performance (e.g., Hinkin et al., 1996; Moore et al., 1997; van Gorp et al., 1991), whereas other studies with broader ranges of cognitive symptoms assessed by the questionnaires and the inclusion of specific domains

of neuropsychological functioning (in particular processing speed and working memory) have obtained modest but significant associations (e.g., Bassel et al., 2002; Mapou et al., 1993; Rourke et al., 1999a). Given the modest effect size, the association between neuropsychological performance and subjective cognitive complaints observed in larger samples (e.g., Carter et al., 2003; Rourke et al., 1999a) was not apparent in this smaller sample of adults with HIV infection.

Clinical Implications and Directions for Future Research

Integration of approaches and dissemination of knowledge across research fields and disciplines is needed to better understand the variable manifestation of *specific* clinical symptoms in individuals with HIV/AIDS. This pilot investigation aimed to accomplish this by integrating biological studies on the neuropathogenesis of HIV within the broader clinical context by exploring potential biological correlates of commonly reported symptoms of cognitive impairments, depression, and chronic fatigue. The major findings were as follows: (1) neuropsychological impairment was *not* associated with serum levels of biological markers; (2) subjective symptoms, particularly the presence and severity of depressive symptoms, were related to some measures of immune activation (i.e., elevated neopterin and mRNA expression of IL-6); and (3) possible non-responders to antidepressant treatment demonstrated elevated immune activation (i.e., higher mean serum neopterin levels in "non-responders" as compared with "responders"). While these preliminary findings require replication in a larger sample, they underscore the importance of considering multiple etiological factors when interpreting and managing clinical symptoms on an individual basis. Although the exact mechanisms underlying these associations cannot be derived from the current analyses, this study

provides support for the role of biological processes (either on their own or as mediators of psychological factors) in the differential expression of clinical symptoms in HIV. More specifically, elevated serum neopterin levels (measured after the attainment of therapeutic drug concentrations) may serve to differentiate depressed individuals that are less likely to respond to antidepressant medications and consequently at greater risk of developing chronic depression.

The behavioural changes frequently accompanying chronic depression have significant implications at individual, clinical, and broader social levels. Chronic depression can adversely impact functioning in everyday life. Higher levels of comorbid fatigue, cognitive complaints, and general illness symptoms (e.g., headaches, pain, decreased appetite, and weight loss) in depressed individuals may further exacerbate their functional limitations. Some depressed individuals may not have the physical and mental stamina to sustain full-time employment. Financial constraints associated with disability status may place them in suboptimal living conditions. Deteriorations in physical health may also result from poor medication adherence or lifestyle changes (e.g., limited exercise, poor diet, or sleep disturbances). As depressed individuals often withdraw from social contacts, they are forced to face life's challenges alone. Mounting psychological stress without supportive outlets may fuel depressive symptomatology. Alternatively, substance abuse or engagement in risky sexual behaviours may be used as a means to superficially cope with the depression and negative views of themselves or others. These practices can be particularly dangerous given their links to the transmission of HIV. Furthermore, depressed individuals may maximally utilize health care services in attempts to manage their psychological and physical discomfort. Clinicians may have

difficulty detecting comorbid medical conditions as depressive symptoms may exaggerate certain illness symptoms while masking others. For example, routine screenings for depression, fatigue, and somatic symptoms need to be directly incorporated into neuropsychological assessments of individuals with HIV in order to assess the full significance of self-reported cognitive symptoms in everyday life.

Early identification of antidepressant-resistant patients (i.e., those individuals with elevated neopterin levels and depressive symptoms after a few weeks of treatment) would allow clinicians to design and implement alternative interventions (e.g. stress management techniques/ psychotherapy alone or in combination with drug therapies) aimed at alleviating their depressive symptoms and ultimately improving their quality of life. Given the widespread clinical and social implications of chronic depression, additional research exploring possible biological and psychological explanations for the differential response to antidepressants in this subgroup is warranted: Do these individuals have greater rates of drug metabolism, quicker degradation of neurotransmitters at synapses, or overstimulation of enzymes that regulate the production of neurotransmitters? Have these individuals suffered from longstanding depression (i.e., prior to their diagnosis of HIV)? Do they have a normal HPA axis response to stress or is their hormonal/immune system abnormal due to prolonged chronic stress? Can functional differences be observed in certain brain regions? Do they operate via specific coping strategies (e.g., avoidance or negative thinking) that are modifiable by cognitive behavioural therapy? Can psychosocial factors (e.g., social support) modify this interaction? Examination of biological factors pre- and post-interventions may also assist in monitoring the progress of susceptible individuals and may provide a better

understanding of the characteristics that affect differential responses to antidepressant treatment. Prospective research designs that examine the progression of symptoms and monitor biological changes at regular time intervals may be particularly fruitful in tracking the pattern of associations. To date, studies on antidepressant effects (including the present investigation) have been limited by confounding factors. Future research should attempt to control for the type of antidepressant (i.e., examining the effects of one antidepressant rather than a mixture of antidepressants) and the duration of treatment. As well, individual differences rather than group means may provide more insight into the characteristics of this subsample. During enrolment in the study, it will be important to define and carefully monitor potential biological changes in response to naturally occurring stressful transitions points during the course of HIV (e.g., diagnosis of HIV seropositive status, initiation of HAART, or diagnosis of AIDS) or in response to unpredictable life stressors (e.g., job loss, breakup of a close relationship, or death of a family member). Given that variations in the production and cyclic regulation of hormones exists between the sexes, attention should also be devoted to controlling for sex differences as well as daily, monthly, and seasonal variations. The collection of multiple samples over the course of the day or in response to experimental stimulation of the immune/HPA systems (e.g., lipopolysaccharide challenge, exposure to psychological stressors, or under dexamethasone suppression) may prove to be more sensitive measures of biological processes than the isolated serum samples used in the present study. While the preliminary findings with IL-6 mRNA expression and neopterin levels are intriguing, verification of these results in a larger follow-study is needed. Future investigations may wish to expand the psychoneuroimmunological framework to incorporate the role of

neurotransmitters. Examination of neurotransmitter levels directly and indirectly through precursor or metabolite concentrations or the activity of enzymes responsible for its production and degradation would provide supplemental information about the possible biological mechanisms underlying symptom expression. Furthermore, advancements in functional imaging techniques may permit the direct evaluation of metabolism or neurotransmitter function within specific regions (e.g., hypothalamus, hippocampus, and prefrontal cortex) that contain higher densities of immune/endocrine receptors and have been proposed to mediate "illness behaviours."

APPENDIX A: Preliminary Analyses of HAART-stable participants

Participants

Data was collected for fifteen individuals on a stable HAART regimen for at least 1 ½ years (i.e., HAART-stable). Two individuals were removed from the analyses because they met one or more of the study exclusionary criteria (see pg. 48). Demographic data for the HAART-stable group are summarized in Table 14. The sample was comprised of all males. Participants were predominantly Caucasian (61%) with the majority reporting sexual contact (77%) as a major risk factor for HIV infection. Mean age, education, recent CD4, and recent CD8 were not different between the HAART-naïve and HAART-stable groups. The groups differed in terms of mean lowest CD4 T cell counts [t (1, 39) = 2.69, $p < .01$], recent viral load log [t (1, 40) = 4.16, $p < .001$], and estimated reading level [t (1, 40) = 2.05, $p < .05$]. The distribution of individuals across CDC disease stages (CDC: Centers for Disease Control and Prevention, 1992) also differed between the HAART-naïve and HAART-stable groups. Individuals in the HAART-stable group were at more advanced disease stages: none were asymptomatic (0%), 4 were mildly symptomatic (30%), and 9 had AIDS-defining illnesses or a nadir CD4 count of less than 200 (70%).

The means and standard deviations for the biological indicators, symptom measures, and neuropsychological deficit scores are presented in Table 15. The distribution across levels of impairment on the total and domain-specific neuropsychological deficit scores were similar within the HAART-naïve and HAART-stable groups, though a greater proportion of individuals within the HAART-stable group demonstrated moderately to severely impaired performance on the learning efficiency

domain (compare Tables 7 and 16). This is further reflected in a greater mean learning deficit for the HAART-stable as compared with the HAART-naïve group [t (1, 42) = -1.98, $p < .05$]. No differences were observed between the mean values on any other measures for the HAART-naïve and HAART-stable groups (see Table 15).

Table 14

Demographics for the HAART-stable sample (N =13)

Variables	Mean (Standard Deviation)
Age (years)	39.8 (9.4)
Education (years)	13.5 (2.0)
WRAT reading (SS)	95.4 (8.9)
Recent CD8 Count	1123.2 (515.4)
Recent CD4 Count	412.5 (312.8)
Lowest CD4 Count	224.3 (226.2)
Recent Viral Load Log	2.1 (1.7)

Table 15

Mean and standard deviations of the biological indicators, symptom measures, and neuropsychological deficit scores in the HAART-stable sample (N =13)

Variables	Mean (Standard Deviation)
TNF-alpha mRNA	828.6 (388.3)
IL-6 mRNA	164.3 (131.9)
TNF-alpha Elisa	7.6 (1.1)
IL-6 Elisa	0.6 (0.5)
Neopterin Elisa	7.3 (5.0)
Cortisol Elisa	339.5 (130.5)
BDI Cognitive-Affective[1]	7.6 (7.5)
Piper Fatigue Total[1]	3.3 (2.7)
PAOF Total[1]	38.9 (17.5)
PAOF Memory[1]	13.6 (7.0)
Illness Total[1]	29.6 (16.8)
Total[2]	0.98 (0.7)
Processing Speed[2]	0.48 (0.7)
Working Memory/Attention[2]	0.15 (0.4)
Learning[2]	2.31 (1.3)

[1]Raw scores; [2]Composite deficit ratings
Note. BDI = Beck Depression Inventory; PAOF = Patient Assessment of Own Functioning Questionnaire

Table 16

Frequencies of individuals within impairment ranges across total and domain-specific neuropsychological deficit indices for the HAART-stable sample (n = 13)

	Total	Processing Speed	Working Memory	Learning Efficiency
Level of Impairment	n (%)	n (%)	n (%)	n (%)
Average	3 (23)	9 (69)	11 (84)	3 (23)
Mild	7 (54)	3 (23)	2 (15)	4 (31)
Mild to Moderate	3 (23)	1 (8)	0 (0)	2 (15)
Moderate	0 (0)	0 (0)	0 (0)	3 (23)
Moderate to Severe	0 (0)	0 (0)	0 (0)	1 (8)
Severe	0 (0)	0 (0)	0 (0)	0 (0)

Associations between biological indicators, symptom measures, and neuropsychological performance

Spearman correlations were separately performed between the biological indicators, symptom measures, and neuropsychological deficit ratings for the HAART-stable group (see Table 17). However, the analyses are described in terms of interesting patterns rather than significant findings per se given the small sample size (n = 13). For comparative purposes, individual subjects are plotted for each of the six biological indicators across total neuropsychological deficit scores (Figures 12 to 17). As shown in Figures 14 and 15, serum IL-6 (i.e., < 11 pg/ml) and TNF-alpha concentrations (i.e., < 20 pg/ml) were well within normal expectations for all individuals. With the exception of one or possibly two individuals, IL-6 and TNF-alpha mRNA expression were also tightly clustered (see Figure 12 and 13). This limited variability of these measures in the HAART-stable group makes it difficult to examine any relative differences across the symptom and neuropsychological measures. In contrast, there are a few cases above the clinical reference ranges for both serum neopterin (i.e., > 10 nmol/L) and cortisol (i.e., > 375 nmol/L) (see Figures 16 and 17). Interestingly, all three participants with clinically elevated neopterin levels showed at least mild to moderate impairment on the total and learning efficiency deficit ratings. All three individuals with clinically elevated cortisol levels also demonstrated at least mild to moderate impairment on the total and learning efficiency domains. No consistent pattern was apparent for these individuals across the symptom measures.

Table 17

Spearman correlations (r_s) showing the association of the biological indicators and measures of depression, fatigue, cognitive symptoms, and neuropsychological deficit ratings within the HAART-stable sample (N = 13)

	TNF-alpha mRNA	IL-6 mRNA	TNF-alpha Elisa	IL-6 Elisa	Neopterin Elisa	Cortisol Elisa
BDI Cog-Aff[1]	0.30	-0.36	0.02	0.37	0.35	-0.22
Piper Fatigue Total[1]	-0.03	0.22	0.16	-0.05	-0.29	-0.13
PAOF Total[1]	0.02	-0.18	-0.05	0.38	0.03	-0.32
PAOF Memory[1]	0.07	-0.61*	-0.09	0.25	0.10	-0.27
Illness Total[1]	-0.02	0.02	0.03	0.26	-0.02	0.00
Total[2]	0.21	-0.16	0.25	0.25	0.48*	0.35
Processing Speed[2]	0.32	0.08	0.22	0.38	0.22	0.10
WM/Attn[2]	0.00	0.19	-0.06	0.33	0.17	0.57*
Learning[2]	0.20	-0.28	0.21	0.15	0.48*	0.27

[1]Raw scores; [2]Composite deficit ratings

*p < .05 (1-tailed), **p< .01 (1-tailed)

Note. BDI Cog-Aff = Beck Depression Inventory Cognitive-Affective score; PAOF = Patient Assessment of Own Functioning Questionnaire; WM/Attn = Working Memory and Attention

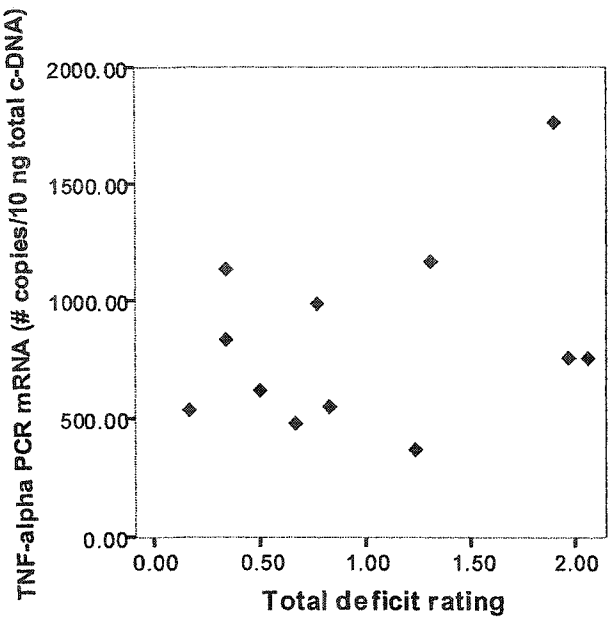

Figure 12. Scatterplot showing the relations between TNF-alpha mRNA expression and total neuropsychological deficit ratings in the HAART-stable sample.

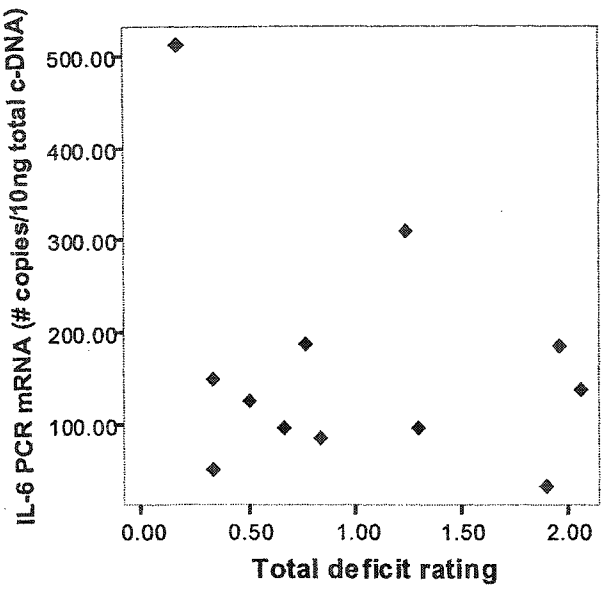

Figure 13. Scatterplot showing the relations between IL-6 mRNA expression and total neuropsychological deficit ratings in the HAART-stable sample.

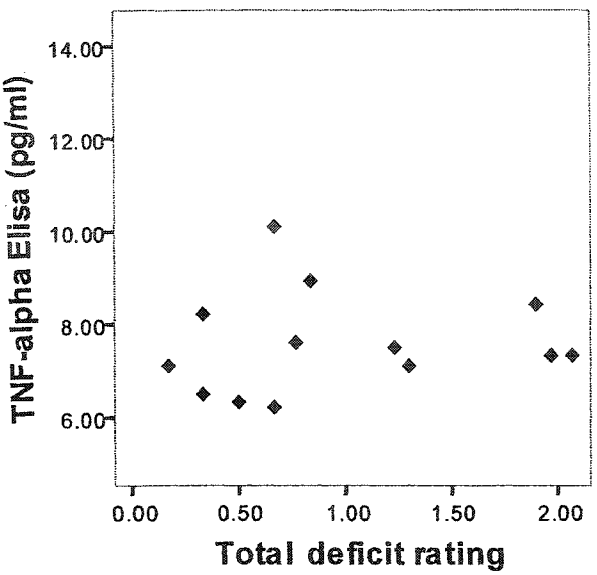

Figure 14. Scatterplot showing the relations between serum TNF-alpha concentrations and total neuropsychological deficit ratings in the HAART-stable sample.

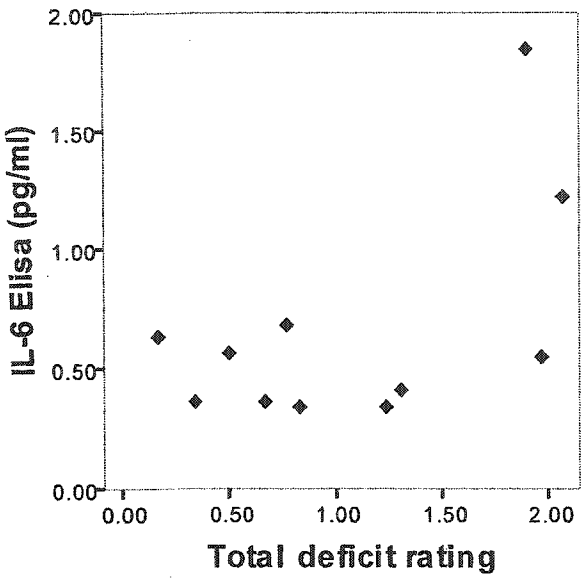

Figure 15. Scatterplot showing the relations between serum IL-6 concentrations and total neuropsychological deficit ratings in the HAART-stable sample.

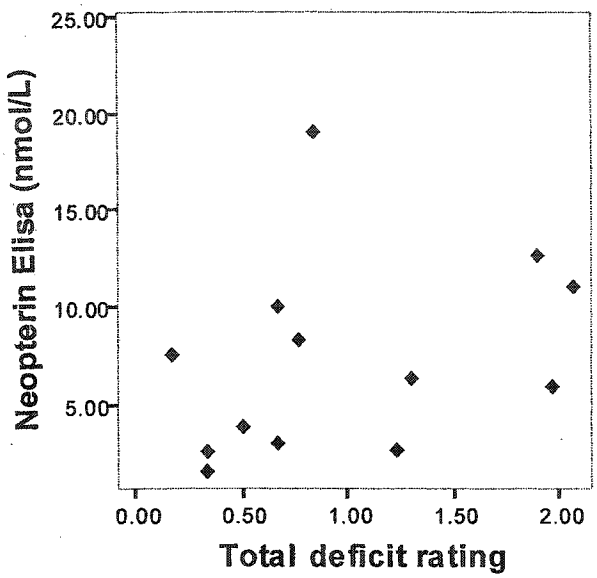

Figure 16. Scatterplot showing the relations between serum neopterin concentrations and total neuropsychological deficit ratings in the HAART-stable sample.

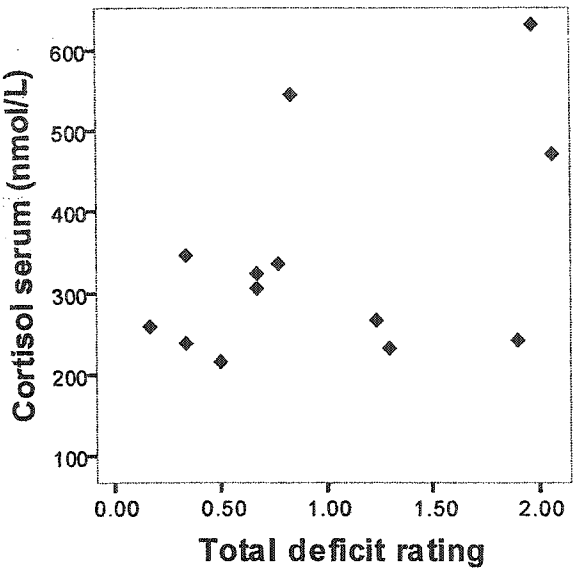

Figure 17. Scatterplot showing the relations between serum cortisol concentrations and total neuropsychological deficit ratings in the HAART-stable sample.

References

Adle-Biassette, H., Chretien, F., Wingertsmann, L., Hery, C., Ereau, T., Scaravilli, F., Tardieu, M., & Gray, F. (1999). Neuronal apoptosis does not correlate with dementia in HIV infection but is related to microglial activation and axonal damage. *Neuropathology and Applied Neurobiology, 25 (2)*, 123-133.

Ahlberg, K., Ekman, T., & Gaston-Johansson, F. (2004). Levels of fatigue compared to levels of cytokines and hemoglobin during pelvic radiotherapy: A pilot study. *Biological Research for Nursing, 5 (3)*, 203-210.

Ahmad, S. (2004). *Neuropsychological differentiation of children and adults with and without non-psychotic unipolar Major Depressive Disorder*. Unpublished doctoral dissertation, Univeristy of Windsor, Ontario.

Albert, S. M., Marder, K., Dooneief, G., Bell, K., Sano, M., Todak, G., & Stern, Y. (1995). Neuropsychologic impairment in early HIV infection: A risk factor for work disability. *Archives of Neurology, 52 (5)*, 525-530.

Albert, S. M., Weber, C. M., Todak, G., Polanco, C., Clouse, R., McElhiney, M., Rabkin, J., Stern, Y., & Marder, K. (1998). An observed performance test of medication management ability in HIV: Relation to neuropsychological status and medication adherence outcomes. *AIDS and Behavior, 3*, 121-128.

Alderson, A. L., & Novack, T. A. (2002). Neurophysiology and clinical aspects of glucocorticoids and memory: A review. *Journal of Clinical and Experimental Neuropsychology, 24 (3)*, 335-355.

Alexander, G. E., DeLong, M. R., & Strick, P. L. (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annual Review of Neuroscience, 9*, 357-381.

Alfano, M., & Poli, G. (2001). Cytokine and chemokine based control of HIV infection and replication. *Current Pharmaceutical Design, 7*, 993-1013.

Altindag, Z. Z., Sahin, G., Isimer, A., Akpek, G., & Kansu, E. (1999). Dihydropteridine reductase activity and neopterin levels in leukemias and lymphomas: Is there any correlation between these two parameters? *Leukemia & Lymphoma, 35 (3-4)*, 367-374.

Amirayan-Chevillard, N., Tissot-Dupont, H., Obadia, Y., Gallais, H., Mege, J. L., & Capo, C. (2000). Highly active antiretroviral therapy (HAART) and circulating markers of immune activation: Specific effect of HAART on neopterin. *Clinical and Diagnostic Laboratory Immunology, 7 (5)*, 832-834.

Andersson, L. M., Hagberg, L., Fuchs, D., Svennerholm, B., & Gisslen, M. (2001). Increased blood-brain barrier permeability in neuro-asymptomatic HIV-1 infected individuals—correlation with cerebrospinal fluid HIV-1 RNA and neopterin levels. *Journal of Neurovirology, 7 (6)*, 542-547.

Andrys, C., Krejsek, J., Slezak, Drahosova, M., & Kopecky, O. (1999). Serum soluble adhesion molecules (sICAM-1, sVCAM-1, sE-selectin) and neopterin in patients with Sjorgen's syndrome [abstract only]. *Acta Medica, 42 (3),* 97-101.

Anisman, H., Ravindran, A. V., Griffiths, J., & Merali, Z. (1999). Endocrine and cytokine correlates of major depression and dysthymia with typical or atypical features. *Molecular Psychiatry, 4*, 182-188.

Antoni, M. H. (2003). Stress management effects on psychological, endocrinological, and immune functioning in men with HIV infection: Empirical support for a psychoneuroimmunological model. *Stress, 6(3)*, 173-188.

Antoni, M. H., Baggett, L., Ironson, G., LaPerriere, A., August, S., Klimas, N., Schneiderman, N., & Fletcher, M. A. (1991). Cognitive-behavioural stress management intervention buffers distress responses and immunological changes following notification of HIV-1 seropositivity. *Journal of Consulting and Clinical Psychology, 59*, 906-915.

Antoni, M. H., Cruess, S., Creuss, D. G., Kumar, M., Lutgendorf, S., Ironson, G., Dettmer, E., Williams, J., Klimas, N., Fletcher, M. A., & Schneiderman, N. (2000). Cognitive-behavioral stress management reduces distress and 24-hour urinary free cortisol output among symptomatic HIV-infected gay men. *Annals of Behavioral Medicine, 22 (1)*, 29-37.

Appels, A. (1999). Inflammation and the mental state before an acute coronary event. *Annals of Medicine, 31*, 41-44.

Appels, A., Bar, F. W., Bar, J., Bruggenman,C., & de Baets, M. (2000). Inflammation, depressive symptomatology, and coronary artery disease. *Psychosomatic Medicine, 62 (5)*, 601-605.

Aukrust, P., Liabakk, N. B., Muller, F., Lien, E., Espevik, T., & Froland, S. S. (1994). Serum levels of tumor necrosis factor-alpha (TNF-alpha) and soluble TNF receptors in human immunodeficiency virus type-1 infection-correlations to clinical, immunologic, and virologic parameters. *Journal of Infectious Diseases, 169 (2)*, 420-424.

Aylward, E. H., Henderer, J. D., McArthur, J. C., Brettschneider, P. D., Harris, G. J., Barta, P. E., & Pearlson, G. D. (1993). Reduced basal ganglia volume in HIV-1-associated dementia: Results from quantitative neuroimaging. *Neurology, 43 (10)*, 2099-2104.

Aylward, E. H. Brettschneider, P. D., McArthur, J. C., Harris, G. J., Schlaepfer, T. E., Henderer, J. D., Barta, P. E., Tien, A. Y., & Pearlson, G. D. (1995). Magnetic resonance imaging of gray matter volume reductions in HIV dementia. *American Journal of Psychiatry, 152 (7)*, 987-994.

Baier-Bitterlich, G., Wachter, H., & Fuchs, D. (1996). Role of neopterin and 7, 8-dihydroneopterin in human immunodeficiency virus infection: Marker for disease progression and pathogenic link. *Journal of Acquired Immune Deficiency Syndrome, 13*, 184-193.

Balbin, E. G., Ironson, G. H., & Solomon, G. F. (1999). Stress and coping: The psychoneuroimmunology of HIV/AIDS. *Balliere's Clinical Endocrinology and Metabolism, 13 (4)*, 615-633.

Barroso, J., Preisser, J. S., Leserman, J., Gaynes, B., Golden, R. N., & Evans, D. N. (2002). Predicting fatigue and depression in HIV-positive gay men. *Psychosomatics, 43 (4)*, 317-325.

Bassel, C., Rourke, S. B., Halman, M. H., & Smith, M. L. (2002). Working memory performance predicts subjective cognitive complaints in HIV infection. *Neuropsychology, 16 (3)*, 400-410.

Basso, M. R., Lowery, N., Neel, J., Purdie, & Bornstein (2002). Neuropsychological impairment among manic, depressed, and mixed episode inpatients with bipolar disorder. *Neuropsychology, 16,* 84-91.

Bateman, A., Singh, A., Kral, T., & Solomon, S. (1989). The immune-hypothalamic-pituitary-adrenal axis. *Endocrine Reviews, 10*, 92-112.

Baxter, J. D., & Tyrell, J. B. (1994). Evaluation of the hypothamic-pituitary-adrenal axis: Importance in steroid therapy, AIDS, and other stress syndromes. *Advances in Internal Medicine, 39*, 667-696.

Beason-Hazen, S., Nasrallah, H. A., & Bornstein, R. A. (1994). Self-report of symptoms and neuropsychological performance in asymptomatic HIV-positive individuals. *Journal of Neuropsychiatry and Clinical Neurosciences, 6*, 43-49.

Beck, A. T., & Steer, R. A. (1993). *Beck Depression Inventory Manual.* San Antonio: The Psychological Corporation.

Bell, J. E. (1998). The neuropathology of adult HIV infection. [abstract only]. *Revue Neurologique, 154 (2),* 816-829.

Benedict, R. H., Mezhir, J. J., Walsh, K., & Hewitt, R. G. (2000). Impact of human immunodeficiency virus type-1 associated cognitive dysfunction on activities of daily living and quality of life. *Archives of Clinical Neuropsychology, 15 (6)*, 535-544.

Berman, M. A., Zaldivar, F., Imfeld, K. L., Kenney, J. S., & Sandborg, C. I. (1994). HIV-1 infection of macrophages promotes long-term survival and sustained release of interleukins 1-alpha and 6. *AIDS Research and Human Retroviruses, 10 (5)*, 529-539.

Bethea, J. R., Chung, I. Y., Sapracio, S. M., Gillespie, G. Y., & Benveniste, E. N. (1992). Interleukin-1 beta induction of tumor necrosis factor-alpha gene expression in human astroglioma cells. *Journal of Neuroimmunology, 36 (2-3)*, 179-191.

Bonaccorso, S., Lin, A. H., Verkerk, R., Van Hunsel, F., Libbrecht, I., Scharpe, S., DeClerck, L., Biondi, M., Janca, A., & Maes, M. (1998). Immune markers in fibromyalgia: Comparison with major depressed patients and normal volunteers. *Journal of Affective Disorders, 48 (1)*, 75-82.

Bornstein, R. A., Nasrallah, H. A., Para, M. F., Fass, R. J., Whitacre, C. C., & Rice, R. R. (1991). Rate of CD4 decline and neuropsychological performance in HIV infection. *Archives of Neurology, 48*, 704-707.

Bornstein, R. A., Nasrallah, H. A., Para, M. F., Whitacre, C. C., Rosenberger, P., & Fass, R. J. (1993). Neuropsychological performance in symptomatic and asymptomatic HIV-1 infection. *AIDS, 7*, 519-524.

Bouwman, F. H., Skolasky, R. L., Hes, D., Selnes, O. A., Glass, J. D., Nance-Sproson, T. E., Royal, W., Dal Pan, G. J., & McArthur, J. C. (1998). Variable progression of HIV-associated dementia. *Neurology, 50 (6)*, 1814-1820.

Bower, J. E., Ganz, P. A., Aziz, N., & Fahey, J. L. (2002). Fatigue and proinflammatory cytokine activity in breast cancer survivors. *Psychosomatic Medicine, 64 (4)*, 604-611.

Brambilla, F., & Maggioni, M. (1998). Blood levels of cytokines in elderly patients with major depressive disorder. *Acta Psychiatrica Scandinavica, 97*, 309-313.

Brenneman, D. E., McCune, S. K., Mervis, R. F., & Hill, J. M. (1994). Gp120 as an etiologic agent for NeuroAIDS: neurotoxicity and model systems. *Advances in Neuroimmunology, 4 (3)*, 157-165.

Brew, B. J., Pemberton, L., Cunningham, P., & Law, M. G. (1997). Levels of human immunodeficiency virus type 1 RNA in cerebrospinal fluid correlate with AIDS dementia stage. *Journal of Infectious Diseases, 175*, 963-966.

Brooke, S., Chan, R., Howard, S., & Sapolsky, R. (1997). Endocrine modulation of the neurotoxicity of gp120: Implications for AIDS-related dementia complex. *Proceedings of the National Academy of Sciences of the USA, 94 (17)*, 9457-9462.

Brooke, S. M., & Sapolsky, R. M. (2000). The effects of steroid hormones in HIV-related neurotoxicity: A mini review. *Biological Psychiatry, 48*, 881-893.

Buffet, R., Agut, H., Chieze, F., Katlama, C., Bolgert, F., Devillechabrolle, A., Diquet, B., Schuller, E., Pierrot-Deseilligny, C., & Gentilini, M. (1991). Virological markers in the cerebrospinal fluid from HIV-1 infected individuals. *AIDS, 5*, 1419-1424.

Buchwald, D., Wener, M. H., Pearlman, T., & Kith, P. (1997). Markers of inflammation and immune activation in chronic fatigue syndrome. *Journal of Rheumatology, 24 (2)*, 372-376.

Burt, D. B., Zembar, M. J., & Niederehe, G. (1995). Depression and memory impairment: a meta-analysis of the association, its pattern, and specificity. *Psychological Bulletin, 117,* 285-305.

Cannon, J. G., Angel, J. B., Ball, R. W., Abad, L.W., Fagioli, L., & Komaroff, A. L. (1999). Acute phase responses and cytokine secretion in chronic fatigue syndrome. *Journal of Clinical Immunology, 19 (6)*, 414-421.

Carey, C. L., Woods, S. P., Gonzalez, R., Conover, E., Marcotte, T. D., Grant, I., Heaton, R. K., & the HNRC Group. (in press). Predictive validity of Global Deficit Scores in detecting neuropsychological impairment in HIV infection. *Journal of Clinical and Experimental Neuropsychology.*

Carpenter, C. C., Cooper, D. A., Fischl, M. A. Gatell, J. M., Gazzard, B. G., Hammer, S. M., Hirsch, M. S., Jacobsen, D. M., Katzenstein, D. A., Montaner, J. S., Richman, D. D., Saag, M. S., Schechter, M., Schooley, R. T., Thompson, M. A., Vella, S., Yeni, P. G., & Volberding, P. A.. (2000). Antiretroviral therapy in adults: Updated recommendations of the international AIDS Society-USA panel. *Journal of the American Medical Association, 283 (3)*, 381-390.

Carpenter, L L., Heninger, G. R., Malison, R. T., Tyrka, A. R., & Price, L. H. (2004). Cerebrospinal fluid interleukin (IL)-6 in unipolar major depression. *Journal of Affective Disorders, 79*, 285-289.

Center for Disease Control. (CDC, 1992). 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *Morbidity and Mortality Weekly Report, 41*, (Suppl. RR-17), 1-19.

Carter, S. L., Rourke, S. B., Murji, S., & Shore, D. (2003). Cognitive complaints, depression, medical symptoms, and their association with neuropsychological functioning in HIV infection: A structural equation model analysis. *Neuropsychology, 17 (3)*, 410-419.

Chaisson, R. E. (1998). The changing natural history of HIV/AIDS in the HAART era: Clinical implications. *Medscape HIV/AIDS, 4, 2.*

Chang, L., Ernst, T., Leonido-Yee, M., & Speck, O. (2000). Perfusion MRI detects rCBF abnormalities in early stages of HIV-cognitive motor complex. *Neurology, 54 (2)*, 389-396.

Chang, L., Ernst, T., Witt, M. D., Ames, N., Gaiefsky, M., & Miller, E. (2002). Relationships among brain metabolites, cognitive function, and viral loades in antiretroviral-naïve HIV patients. *Neuroimage, 17 (3)*, 1638-1648.

Chelune, G. J., Heaton, R. K., & Lehman, R. A. W. (1986). Neuropsychological and personality correlates of patients' complaints of disability. In R. E. Tarter & G. Goldstein (Eds). *Advances in clinical neuropsychology, Vol. 3.* (pp. 95-126), New York, NY: Plenum Press.

Childs, E. A., Lyles, R. H., Selnes, O. A., Chen, B., Miller, E. N., Cohen, B. A., Becker, J. T., Mellors, J., & McArthur, J. C. (1999). Plasma viral load and CD4 lymphocytes predict HIV-associated dementia and sensory neuropathy. *Neurology, 52*, 607-613.

Christeff, N., Michon, C., Goertz, G., Hassid, J., Matheron, S., Girard, P. M., Couland, J. P., & Nunez, E. A. (1988). Abnormal free fatty acids and cortisol concentrations in the serum of AIDS patients. *European Journal of Cancer and Clinical Oncology, 24 (7),* 1179-1183.

Ciesla, J. A., & Roberts, J. E. (2001). Meta-analysis of the relationship between HIV infection and risk for depressive disorders. *American Journal of Psychiatry, 158 (5)*, 725-730.

Cleare, A. J., O'Keane, V., & Miell, J. P. (2004). Levels of DHEA and DHEAS and responses to CRH stimulation and hydrocortisone treatment in fatigue syndrome. *Psychoneuroendocrinology, 29 (6)*, 724-732.

Cleary, P. D., Fowler, F. J., Weissman, J., Massagli, M. P., Wilson, I., Seage, G. R., Gatsonis, C., & Epstein, A. (1993). Health-related quality of life in persons with acquired immune deficiency syndrome. *Medical Care, 31 (7)*, 569-580.

Clerici, M., Fusi, M. L., Ruzzante, S., Piconi, S., Biasin, D. A., Trabattoni, D., & Villa, M. L. (1997a). Type 1 and type 2 cytokines in HIV infection-A possible role in apoptosis and disease progression. *Annals of Medicine, 29*, 185-188.

Clerici, M., Trabattoni, D., Piconi, S., Fusi, M. L., Ruzzante, S., Clerici, C., & Villa, M. L. (1997b). A possible role for the cortisol/anticortisols imbalance in the progression of human immunodeficiency virus. *Psychoneuroendocrinology, 22 (Suppl. 1)*, 27-31.

Cole, S. W., Kemeny, M. E., Fahey, J. L., Zack, J. A., & Naliboff, B. D. (2003). Psychological risk factors for HIV pathogenesis: Mediation by the autonomic nervous system. *Biological Psychiatry, 54 (12)*, 1444-1456.

Corley, P. A. (1995). HIV and the cortisol connection: A feasible concept of the process of AIDS. *Medical Hypotheses, 44*, 483-489.

Cummings, J. L. (1993). Frontal-subcortical circuits and humans behaviour. Archives of *Neurology, 50 (8)*, 873-880.

Cupps, T., & Fauci, A. (1982). Corticosteroid-mediated immunoregulation in man. *Immunology Reviews, 65*, 133-155.

Dal Pan, D. J., Farzadegan, H., Selnes, O., Hoover, D. R., Miller, E. N., Skolasky, R. L., Nance-Sproson, T. E., & McArthur, J. C. (1998). Sustained cognitive decline in HIV infection: Relationship to CD4+ cell count, plasma viremia and p24 antigenemia. *Journal of Neurovirology, 4 (1)*, 95-99.

da Silva, B., Singer, W., Fong, I. W., & Ottaway, C. A. (1999). In vivo cytokine and endocrine responses to endotoxin in human immunodeficiency virus-infected subjects. *Journal of Infectious Diseases, 180*, 106-115.

Davis, L. E., Hjelle, B. L., Miller, V. E., Palmer, d. L., Llewellyn, A. L., Merlin, T. L., Young, S. A., Mills, R. G., Wachsman, W., & Wiley, C. A. (1992). Early viral brain invasion in iatrogenic human immunodeficiency virus infection. *Neurology, 42*, 1736-1739.

Decker, D., Schondorf, M., Bidlingnaier, F., Hirner, A., & von Ruecker, A. A. (1996). Surgical stress induces a shift in the type-1/type-2 T-helper cell balance, suggesting down-regulation of cell-mediated and up-regulation of antibody-mediated immunity commensurate to the trauma. *Surgery, 119 (3)*, 316-325.

Denburg, S. D., Carbotte, R. M., & Denburg, J. A. (1997). Psychological aspects of systemic lupus erythematosus: Cognitive function, mood, and self report. *Journal of Rheumatology, 24*, 998-1033.

Detels, R., Visscher, B. R., Fahey, J. L., Sever, J. L., Gravell, M., Madden, D. L., Schwartz, K., Dudely, J. P., English, P. A., & Powers, H. (1987). Predictors of clinical AIDS in young homosexual men in a high risk area. *International Journal of Epidemiology, 16*, 271-276.

Dolan, M. J., Clerici, M., Blatt, S. P., Hendrix, C. W., Melcher, G. P., Boswell, R. N., Freeman, T. M., Ward, W., Hensley, R., & Shearer, G. M. (1995). In vitro T cell function, delayed type hypersensitivity skin testing, and CD4 T cell subset phenotyping independently predict survival time in patients infected with human immunodeficiency virus. *Journal of Infectious Diseases, 172 (1)*, 79-87.

Dunbar, P. R., Hill, J., Neale, T. J., & Mellsop, G. W. (1992). Neopterin measurement provides evidence of altered cell-mediated immunity in patients with depression, but not with schizophrenia. *Psychological Medicine, 22*, 1051-1057.

Eichenbaum, H. (1999). The hippocampus and mechanisms of declarative memory. *Behavioural Brain Research, 103*, 123-133.

Elenkov, I., Papanicolaon, D., Wilder, R., & Chrousos, G. P. (1996). Modulatory effects of glucocorticoids and catecholamines on human interleukin-12 and interleukin-10 production: Clinical implications. *Proceedings of the Association of American Physicians, 108*, 334-381.

Ellis, R. J., Deutsch, R., Heaton, R. K., Marcotte, T. D., McCutchan, J. A., Nelson, J. A., Abramson, I., Thal, L. J., Atkinson, J. H., Wallace, M. R., & Grant, I. (1997).

Cognitive impairment is an independent risk factor for death in HIV infection. *Archives of Neurology, 54 (4)*, 416-424.

Elovaara, I., Poutianinen, E., Raininko, R., Valanne, L., Virta, A., Valle, S. L., Lahdevirta, J., & Iivananinen, M. (1990). Mild brain atrophy in early HIV-1 infection: The lack of association with cognitive deficits and HIV-specific intrathecal immune response. *Journal of the Neurological Sciences, 99*, 121-136.

Errico, A. L., King, A. C., Lovallo, W. R., & Parsons, O. A. (2002). Cortisol dysregulation and cognitive impairment in abstinent male alcoholics. *Alcoholism: Clinical and Experimental Research, 26 (8)*, 1198-1204.

Everall, I. P., Heaton, R. K., Marcotte, T. D., Ellis, R. J., McCutchan, J.A., Atkinson, J. H., Grant, I., Mallory, M., & Mashliah, E (1999). Cortical synaptic density is reduced in mild to moderate human immunodeficiency virus cognitive disorder. HNRC group. HIV Neurobehavioural Research Center. *Brain Pathology, 9 (2)*, 209-217.

Fahey, J. L., Taylor, J. M., Detels, R., Hofmann, B., Melmed, R., Nishanian, P., & Giorgi, J. (1990). The prognostic value of cellular and serologic markers in infection with human immunodeficiency virus Type 1. *New England Journal of Medicine, 322 (3)*, 166-172.

Fahey, J. L., Taylor, J. M., Manna, B., Nishanian, P., Aziz, N., Giorgi, J. V., & Detels, R. (1998). Prognostic significance of plasma markers of immune activation, HIV viral load and CD4 T-cell measurements. *AIDS, 12 (13)*, 1581-1590.

Farzadegan, H., Chmiel, J. S., Odaka, N., Ward, L., Poggensee, L., Saah, A., & Phair, J. P. (1992). Association of antibody to human immunodeficiency virus type 1 core

protein (p24), CD4+ lymphocyte number, and AIDS-free time. *Journal of Infectious Diseases, 166*, 1217-1222.

Fauci, A. S. (1996). Host factors and the pathogenesis of HIV-induced disease. *Nature, 384 (6609)*, 529-534.

Ferrando, S., Evans, S., Goggin, K., Sewell, M., Fishman, B., & Rabkin, J. (1998). Fatigue in HIV illness: Relationship to depression, physical limitations, and disability. *Psychosomatic Medicine, 60 (6)*, 759-764.

Fell, M., Newman, S., Herns, M., Durrance, P., Manji, H., Connolly, S., McAlister, R., Weller, I., & Harrison, M. (1993). Mood and psychiatric disturbance in HIV and AIDS: Changes over time. *British Journal of Psychiatry, 162*, 604-610.

Fiala, M., Looney, D. J., Stins, M., Way, D. D., Zhang, L., Gan, X., Chiappelli, G., Schweitzer, E. S., Shapshak, P., Weinand, M., Graves, M. C., Witte, M., & Kim, K. S. (1997). TNF-alpha opens a paracellular route for HIV-1 invasion across the blood brain barrier. *Molecular Medicine, 3*, 553-564.

Fijumura, R. K., Goodkin, K., Petito, C. K., Douyon, R., Feaster, D. J., Concha, M., & Shapshak, P. (1997). HIV-1 proviral DNA load across neuroanatomic regions of individuals with evidence for HIV-1 associated dementia. *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology, 16 (3)*, 146-152.

Findling, J. W., Buggy, B. P., Gilson, I. H., Brummitt, C. F., Bernstein, B. M., & Raff, H. (1994). Longitudinal evaluation of adrenocortical function in patients infected with the human immunodeficiency virus. *Journal of Endocrinology and Metabolism, 79 (4)*, 1091-1096.

Fine, S. M., Angel, R. A., Perry, S. W., Epstein, L. G., Rothstein, J. D., Dewhurst, S., & Gelbard, H. A. (1996). Tumor necrosis factor alpha inhibits glutamate uptake by primary human astrocytes: Implications for pathogenesis of HIV-1 dementia. *Journal of Biological Chemistry, 271 (26)*, 15303-15306.

Flachenecker, P., Bihler, I., Weber, F., Gottschalk, M., Toyka, K. V., & Rieckman, P. (2004). Cytokine mRNA expression in patients with multiple sclerosis and fatigue. *Multiple Sclerosis, 10 (2)*, 165-169.

Fleishman, J. A., & Crystal, S. (1998). Functional status transitions and survival in HIV disease: Evidence from the AIDS Costs and Service Utilization Survey. *Medical Care, 36 (4)*, 533-543.

Fossati, P., Deweer, B., Raoux, N., & Allilaire, J. F., (1995). Deficits of recall in depressed patients. Evidence for a subcortical dysfunction in major depression. *Encephale,* 21, 295-305.

Frommberger, U. H., Bauer, J., Haselbauer, P., Fraulin, A., Riemann, D., & Berger, M. (1997). Interleukin-6 (IL-6) plasma levels in depression and schizophrenia: Comparison between the acute state and after remission. *European Archives of Psychiatry and Clinical Neurosciences, 247*, 228-233.

Fuchs, D., Spira, T. J., Hausen, A., Reibnegger, G., Werner, E. R., Werner Felmayer, G., & Wachter, H. (1989). Neopterin as a predictive marker for disease progression in human immunodeficiency virus type 1 infection. *Clinical Chemistry, 35*, 1746-1749.

Gallo, R. C., Salahuddin, S. Z., Popovic, M., Shearer, G., Kaplan, M., Haynes, B. F., Parker, T. J., Redfield, R., Oleske, J., & Safai, B. (1984). Frequent detection and

isolation of cytopathic retroviruses (HTLV-III) from patients with AIDS and at risk for AIDS. *Science, 224 (4648),* 500-503.

Geinitz, H., Zimmermann, F. B., Stoll, P., Thamm, R., Kaffenberger, W., Anson, K., Keller, M., Busch, R., van Beuningen, D., & Molls, M. (2001). Fatigue, serum cytokine levels, and blood cell counts during radiotherapy of patients with breast cancer. *International Journal of Radiation Oncology, Biology, Physics, 51(3),* 691-698.

Gendelman, H. E., Lipton, S. A., Tardieu, M., Bukrinsky, M. I., & Nottet, H. S. L. M. (1994). The neuropathogenesis of HIV-1 infection. *Journal of Leukocyte Biology, 56 (3),* 389-398.

Genis, P., Jett, M., Bernton, E. W., Boyle, T., Gelbard, H. A., Dzenko, K., Keane, R. W., Resnick, L., Mizrachi, Y., Volsky, D. J., Epstein, L. G., & Gendelman, H. E. (1992). Cytokines and arachidonic metabolites produced during human immunodeficiency virus (HIV)-infected macrophages-astroglia interactions: Implications for the neuropathogenesis of HIV disease. *Journal of Experimental Medicine, 176 (6),* 1703-1718.

Gershon, A. S., Margulies, M., Gorczynski, R. M., & Heathcote, E. J. (2000). Serum cytokine values and fatigue in chronic hepatitis C infection. *Journal of Viral Hepatology, 7 (6),* 397-402.

Gibbs, A., Andrewes, D. G., Szmukler, G., Mulhall, B., & Bowden, S. C. (1990). Early HIV-related neuropsychological impairment: Relationship to stage of viral infection. *Journal of Clinical and Experimental Neuropsychology, 12 (5),* 766-780.

Giovannoni, G., Lai, M., Kidd, d., Thorpe, J. W., Miller, D. H., Thompson, . J., Keir, G., Feldmann, M., & Thompson, E. J. (1997). Daily urinary neopterin excretion as an immunological marker of disease activity in multiple sclerosis. *Brain, 120*, 1-13.

Giovannoni, G., Thompson, A. J., Miller, D. H., & Thompson, E. J. (2001). Fatigue is not associated with raised inflammatory markers in multiple sclerosis. *Neurology, 57* (4), 676-681.

Glaser, R., Robles, T. F., Sheridan, J., Malarkey, W. B., & Kiecolt-Glaser, J. K (2003). Mild depressive symptoms are associated with amplified and prolonged inflammatory responses after influenza virus vaccination in older adults. *Archives of General Psychiatry, 60 (10)*, 1009-1014.

Godfried, M. H., van der Poll, T., Weverling, G. J., Mulder, J. M., Jansen, J., van Deventer, S. J. H., & Sauerwein, H. P. (1994). Soluble receptors of tumor necrosis factor as predictors of progression to AIDS in asymptomatic human immunodeficiency virus type-1 infection. *Journal of Infectious Diseases, 169*, 739-745.

Goodkin, K., Baldewicz, T. T., Wilkie, F. L., Tyll, M. D., & Shapshak, P. (2001). HIV-1 infection of the brain: A region-specific approach to its neuropathophysiology and therapeutic prospects. *Psychiatric Annals, 31 (3)*, 182-191.

Gorman, J. M., & Kertzner, R. (1990). Psychoneuroimmunology of HIV infection. *Journal of Neuropsychiatry, 2*, 241-252.

Grant, I., & Atkinson, J. H. (1990). The evolution of neurobehavioural complications of HIV-1 infection. *Psychological Medicine, 20 (4)*, 747-754.

Griffin, D. E., McArthur, J. C., & Cornblath, D. R. (1991). Neopterin and interferon-gamma in serum and cerebrospinal fluid of patients with HIV-associated neurologic disease. *Neurology, 41 (1)*, 69-74.

Grimaldi, L. M. E., Martino, G. V., Franciotta, M., Brustia, R., Castagna, A., Pristera, R., & Lazzarin, A. (1991). Elevated alpha-tumor necrosis factor levels in spinal fluid from HIV-1 infected patients with central nervous system involvement. *Annals of Neurology, 29 (1)*, 21-25.

Grinspoon, S. K., & Bilezikian, J. P. (1992). HIV disease and the endocrine system. *New England Journal of Medicine, 327*, 1360-1365.

Gur, A., Karakoc, M., Nas, K., Remzi, Cevik, Denli, A., & Sarac, J. (2002). Cytokines and depression in cases with fibromyalgia. *Journal of Rheumatology, 29 (2)*, 358-361.

Gur, A., Remzi, C., Nas, K., Colpan, L., & Sarac, S. (2004). Cortisol and hypothalamic-pituitary-gonadal axis hormones in follicular-phase women with fibromyalgia and chronic fatigue syndrome and effect of depressive symptoms on these hormones. *Arthritis Research and Therapy, 6 (3)*, 232-238.

Guyton, A. C. (1991). *Basic Neuroscience: Anatomy and Physiology (2nd ed.)*. Philadelphia: W. B. Saunders Company.

Hall, M., Whaley, R., Robertson, K., & Hamby, S. (1996). The correlation between neuropsychological and neuroanatomic changes over time in asymptomatic and symptomatic HIV-1 infected individuals. *Neurology, 46 (6)*, 1697-1702.

Hamerlinck, F. F. (1999). Neopterin: A review. *Experimental Dermatology, 8 (3)*, 167-176.

Harrison, M. J., Newman, S. P., Hall-Craggs, M. A., Fowler, C. J., Miller, R., Kendall, B. E., Paley, M., Wilkinson, I., Sweeney, B., Lunn, S., Carter, S., & Williams, I. (1998). Evidence of CNS impairment in HIV infection: Clinical, neuropsychological, EEG, and MRI/MRS study. *Journal of Neurology, Neurosurgery and Psychiatry, 65*, 301-307.

Heaton, R. K., Grant, I, Butters, N., White, D. A., Kirson, D., Atkinson, J. H., McCutchan , J. A., Taylor, M. J., Kelly, M. D., & Ellis, R. J. (1995). The HNRC 500: Neuropsychology of HIV infection at different disease stages. *Journal of the International Neuropsychological Society, 1*, 231-251.

Heaton, R. K., Marcotte, T. D., Mindt, M. R., Sadek, J., Moore, D. J., Bentley, H., McCutchan, J. A., Reicks, C., Grant, I., & HNRC Group. (2004). The impact of HIV-associated neuropsychological impairment on everyday functioning. *Journal of the International Neuropsychological Society, 10 (3)*, 317-331.

Heaton, R. K., Marcotte, T. D., White, D. A., Ross, D., Meredith, K., Taylor, M. J., Kaplan, R., & Grant, I. (1996). Nature and vocational significance of neuropsychological impairment associated with HIV infection. *The Clinical Neuropsychologist, 10*, 1-14.

Heaton, R. K., Velin, R. A., McCutchan, J. A., Gulevich, S. J., Atkinson, J. H., Wallace, M. R., Godfrey, H. P., Kirson, D. A., & Grant, I. (1994). Neuropsychological impairment in human immunodeficiency virus-infection: Implications for employment. HIV Neurobehavioral Research Center. *Psychological Medicine, 56*, 8-17.

Heffelfinger, A. K., & Newcomer, J. W. (2001). Glucocorticoid effects on memory function over the human life span. *Development & Psychopathology. Special Issue: Stress and development: Biological and psychological consequences, 13*, 491-513.

Hestad, K., McArthur, J. H., Dal Pan, G. J., Selnes, O. A., Nance-Sproson, T. E., Aylward, E., Mathews, v. P., & McArthur, J. C. (1993). Regional brain atrophy in HIV-1 infection: Association with specific neuropsychological test performance. *Acta Neurologica Scandinavica, 88 (2)*, 112-118.

Heyes, M. P., Saito, K., Crowley, J. S., Davis, L.E., Demitrack, M. A., Der, M., Dilling, L. A., Elia, J., Kruesi, M. J., & Lackner, A. (1992). Quinolinic acid and kynurenine pathway metabolism in inflammatory and non-inflammatory neurological disease. *Brain, 115*, 1249-1273.

Hinkin, C. H., van Gorp, W. G., Satz, P., Marcotte, T., Durvasula, R. S., Wood, S., Campbell, L., & Baluda, M. R. (1996). Actual versus self-reported cognitive dysfunction in HIV-1 infection: Memory-metamemory dissociations. *Journal of Clinical and Experimental Neuropsychology, 18*, 431-443.

Hogervorst, E., Jurriaans, S., de wolf, F., van Wijk, A., Wiersman, A., Valk, M., Roos, M., van Gemen, B., Coutinho, R., & Miedema, F. (1995). Predictors for non- and slow progression in human immunodeficiency virus (HIV) type 1 infection: Low viral RNA copy numbers in serum and maintenance of high HIV-1 p24-specific but not V3-specific antibody levels. *Journal of Infectious Diseases, 171*, 811-821.

Homo-Delarche, F., Fitzpatrick, F., Christeff, N., Nunex, E. A., Bach, J. F., & Dardenne, M. (1991). Sex steroids, glucocorticoids, stress and autoimmunity. *Journal of Steroid Biochemistry and Molecular Biology, 40 (4-6)*, 619-637.

Honda, M., Kitamura, K., Mizutani, Y., Olshi, M., Araj, M., Okura, T., Igarahi, K., Yasukawa, K., Hirano, T., Kishimoto, T., Mitsuyasu, R., Chermann, J. C., & Tokunaga, T. (1990). Quantitative analysis of serum IL-6 and its correlation with increased levels of serum IL-2R in HIV-induced diseases. *Journal of Immunology, 145 (12)*, 4059-4064.

Howell, D. C. (1999). *Fundamental Statistics for the Behavioural Sciences* (4th Edition). Pacific Grove, CA: Duxbury Press.

Ilonen, T. Taiminen, T., Karlsson, H., Lauerma, H., Tuimala, P., Leinonen, K., Wallenius, E., Salokangas, R. (2000). Impaired Wisconsin Card Sorting Test performance in first-episode severe depression.

Isley, J. E., Moffoot, A. P. R., & O'Carroll, R. E. (1995). An analysis of memory dysfunction in major depression. *Journal of Affective Disorders, 35,* 1-9.

Iyer, A. M., Brooke, S. M., & Sapolsky, R. M. (1998). Glucocorticoids interact with gp120 in causing neurotoxicity in striatal cultures. *Brain Research, 808 (2)*, 305-309.

Jacobson, M.A., Fusaro, R. E., & Galmarini, M., & Lang, W. (1991). Decreased serum dehydroepiandrosterone is associated with an increased progression of human immunodeficiency virus infection in men with CD4 cell counts of 200-499. *Journal of Infectious diseases, 164*, 864-868.

Janeway, C. A., & Travers, P. (1997). *Immunobiology: The immune system in health and disease.* London: Current Biology Ltd/Garland Publishing Inc.

Janssen, R. S., Cornblath, D. R., Epstein, L. G., Foa, R. P., McArthur, J. C., & Price, R. W. (1991). Nomenclature and research case definitions for neurologic manifestations of human immunodeficiency virus-type 1 (HIV-1) infection. *Neurology, 41*, 778-785.

Joyce, D. A., Steer, J. H., & Abraham, L. J. (1997). Glucocorticoid modulation of human monocyte/macrophage function: Control of TNF-alpha secretion. *Research, 46 (11)*, 447-451.

Justice, A. C., Rabeneck, L., Hays, R. D., Wu, A. W., & Bozzette, S. A. (1999). Sensitivity, specificity, reliability, and clinical validity of provider-reported symptoms: A comparison with self-reported symptoms. *Journal of Acquired immune Deficiency Syndrome, 21 (2)*, 126-133.

Kahl, K. G., Kruse, N., Faller, H., Wei, H., & Rieckmann, P. (2002). Expression of tumor necrosis factor-alpha and interferon-gamma mRNA in blood cells correlates with depression scores during an acute attack in patients with multiple sclerosis. *Psychoneuroendocrinology, 27*, 671-681.

Kalichman, S. C., Sikkeman, K. J., & Somlai, A. (1995). Assessing persons with human immunodeficiency virus (HIV) infection using the Beck Depression Inventory: Disease processes and other potential confounds. *Journal of Personality Assessment, 64 (1)*, 86-100.

Kaplan, R. M., Anderson, J. P., Patterson, T. L., McCutchan, J. A., Weinrich, J. D., Heaton, R. K., Atkinson, J. H., Thal, L., Chandler, J., & Grant, I. (1995). Validity

of the Quality of Well-Being Scale for persons with human immunodeficiency virus infection. HIV Neurobehavioral Research Center. *Psychosomatic Medicine, 57 (2)*, 138-147.

Keenan, P. A., Jacobson, M. W., Soleymani, R. M., Mayes, M. D., Stress, M. E., & Yaldoo, D. T. (1996). The effect on memory of chronic prednisone treatment in patients with systemic disease. *Neurology, 47 (6)*, 1396-1402.

Keenan, P. A., Jacobson, M. W., Soleymani, R. M., & Newcomer, J. W. (1995). Commonly used therapeutic doses of glucocorticoids impair explicit memory. *Annals of the New York Academy of Sciences, 761*, 400-402.

Kemeny, M. E. (2003). An interdisciplinary research model to investigate psychosocial cofactors in disease: Application to HIV-1 pathogenesis. *Brain, Behavior, and Immunity, 17*, S62-72.

Kim, D. H., Jewison, D. L., Milner, G. R., Rourke, S. B., Gill, M. J., & Power, C. (2001). Cognitive symptoms and impairment in an HIV community clinic. *Canadian Journal of Neurological Sciences, 28 (3)*, 228-231.

Kirschbaum, C., Wolf, O. T., May, M., Wippich, W., & Hellhammer, D. H. (1996). Stress and treatment-induced elevations of cortisol levels associated with impaired declarative memory in healthy adults. *Life Sciences, 58*, 1475-1483.

Klein, S. A., Dobmeyer, J. M., Dobmeyer, T. S., Pape, M., Ottmann, O. G., Helm, E. B., Hoelzer, D., & Rossol, R. (1997). Demonstration of the Th1 to Th2 cytokine shift during the course of HIV-1 infection using cytoplasmic cytokine detection on single cell level by flow cytometry. *AIDS, 11 (9)*, 1111-1118.

Kozora, E., Laudenslager, M., Lemieux, A., & West, S. G. (2001). Inflammatory and hormonal measures predict neuropsychological functioning in systemic lupus erythematosus and rheumatoid arthritis patients. *Journal of the International Neuropsychological Society, 7*, 745-754.

Kronfol, Z. & Remick, D. G. (2000). Cytokines and the brain: Implications for clinical psychiatry. *American Journal of Psychiatry, 157 (5)*, 683-694.

Kubera, M., Kenis, G., Bosmans, E., Kajta, M., Basta-Kaim, A., Scharpe, S., Budziszewska, B., & Maes, M. (2004). Stimulatory effect of antidepressants on the production of IL-6. *International Immunopharmacology, 4*, 185-192.

Kubera, M., Kenis, G., Bosmans, E., Zieba, A., Dudek, D., Nowak, G., & Maes, M. (2000). Plasma levels of interleukin-6, interleukin-10, and interleukin-1 receptor antagonist in depression: Comparison between the acute state and after remission. *Polish Journal of Pharmacology, 52*, 237-241.

Kulinkovich, A., Englemann, H., Harpaz, N., Burnstein, R., Barak, V., & Kalickman, I. (1992). Elevated serum levels of soluble tumor necrosis factor receptors (sTNF-R) in patients with HIV infection. *Clinical and Experimental Immunology, 89*, 351-355.

Kumar, M., Kumar, A. M., Morgan, R., Szapocznik, J., & Eisdorfer, C. (1993). Abnormal pituitary-adrenocortical response in early HIV-1 infection. *Journal of Acquired Immune Deficiency Syndromes, 6 (1)*, 61-65.

Kumar, M., Kumar, A. M., Waldrop, D., Antoni, M. H., & Eisdorfer, C. (2003). HIV-1 infection and its impact on the HPA axis, cytokines, and cognition. *Stress, 6 (3)*, 167-172.

Kurzrock, R. (2001). The role of cytokines in cancer-related fatigue. *Cancer, 92 (Suppl. 6)*, 1684-1688.

Landro, N. I., Stiles, T. C., & Sletvold, H. (2001). Neuropsychological function in nonpsychotic unipolar major depression. *Neuropsychiatry, Neuropsychology, and Behavioral Neurology, 14,* 233-240.

Lanquillon, S., Krieg, J. C., Bening-Abu-Shach, U., & Vedder, H. (2000). Cytokine production and treatment response in major depressive disorder. *Neuropsychopharmacology, 22 (4)*, 370-379.

Lathey, J. L., Kanangat, S., & Rouse, B. T. (1994). Differential expression of tumor necrosis factor alpha and interleukin-1 beta compared with interleukin 6 in monocytes from human immunodeficiency virus-positive individuals measured by polymerase chain reaction. *Journal of Acquired Immunodeficiency Syndromes, 7 (2)*, 109-115.

Lepage, M., Ghaffar, O., Nybergy, L., & Tulving, E. (2000). Prefrontal cortex and episodic memory retrieval mode. *Proceedings of the National Academy of Sciences of the USA, 97*, 506-511.

Leu, S. J., Shiah, L. S., Yatham, L. N., Cheu, Y. M., & Lam, R. W.(2001). Immune-inflammatory markers in patients with seasonal affective disorder: Effects of light therapy. *Journal of Affective Disorders, 63*, 27-34.

Lin, J. S., Amaral, T. D., Brosnan, C. F., & Lee, S. C. (1998). Interferons as critical regulators of IL-1 receptor antagonist and IL-1 expression in human microglia. *Journal of Immunology, 161 (4),* 1989-1996.

Lopez, O. L., Wess, J., Sanchez, J., Dew, M. A., & Becker, J. T. (1998). Neurobehavioral correlates of perceived mental and motor slowness in HIV infection and AIDS. *The Journal of Neuropsychiatry and Clinical Neurosciences, 10*, 343-350.

Lortholary, O., Chrsiteff, N., Casassus, P., Thobie, N., Veyssier, P., Trogoff, B., Torri, O., Brauner, M., Nunez, E. A., & Guillevin, L. (1996). Hypothalamic-pituitary-adrenal function in human immunodeficiency virus-infected men. *Journal of Clinical Endocrinology and Metabolism, 81 (2)*, 791-796.

Lucey, D. R., Melcher, G. P., Hendrix, C. W., Zajac, R. A., Goetz, G. W., Butzin, C. A., Clerici, M., Warner, R. D., Abbadessa, S., & Hall, K. (1991). The US Air Force HIV study 1985-1990: Immunological analyses, seroconversion and the potential utility of a T helper functional assay to predict change in CD4+ T-cell counts during early stages in HIV infection. *Journal of Infectious Diseases, 164 (4)*, 631-637.

Lupien, S. J., Gillin, C., & Hauger, R. L. (1999). Working memory is more sensitive than declarative memory to the acute effects of corticosteroids: A dose-response study in humans. *Behavioral Neuroscience, 113 (3)*, 420-430.

Maes, M. (1993). Acute phase protein alterations in major depression: A review. *Review in Neuroscience, 4*, 407-416.

Maes, M. (2001). The immunoregulatory effects of antidepressants. *Human Psychopharmacology, 16,* 95-103.

Maes, M., Bosmans, E., Jongh, R. D., Kenis, G., Vandoolaeghe, E., & Neels, H. (1997). Increased serum IL-6 and IL-1 receptor antagonist concentrations in major depression and treatment resistant depression. *Cytokine, 9 (11)*, 853-858.

Maes, M., Meltzer, H. Y., Bosmans, E., Bergmans, R., Vandoolaeghe, E., Ranjan, R., & Desnyder, R. (1995), Increased plasma concentrations of interleukin-6, soluble interleukin-6, soluble interleukin-2 and transferring receptor in major depression. *Journal of Affective Disorders, 34*, 301-309.

Maes, M., Scharpe, S., Meltzer, H. Y., Okayli, G., Bosmans, E., D'Hondt, P., Vanden Bossche, B., & Cosyns, P. (1994). Increased neopterin and interferon gamma secretion and lower availability of L-tryptophan in major depression: Further evidence for activation of cell-mediated immunity. *Psychiatry Research, 54*, 143-160.

Maes, M., Song, C., Lin, A. H., Bonaccorso, S., Kenis, G., De Jongh, R., Bosmans, E., & Scharpe, S. (1999). Negative immunoregulatory effects of antidepressants: Inhibition of interferon-gamma and stimulation of interleukin-10 secretion. *Neuropsychopharmacology, 20 (4)*, 370-379.

Maier, S. F., Goehler, L. E., Fleshner, M., & Watkins, L. R. (1998). The role of the vagus nerve in cytokine-to-brain communication. *Annals of the New York Academy of Sciences, 840,* 289-300.

Maier, S. F., & Watkins, L. R. (1998). Cytokines for Psychologists: Implications of bidirectional immune-to-brain communication for understanding behaviour, mood, and cognition. *Psychological Review, 105 (1)*, 83-107.

Maier, S. F., Watkins, L. R., & Fleshner, M. (1994). Psychoneuroimmunology: The interface between behaviour, brain, and immunity. *American Psychologist, 49*, 1004-1018.

Maimone, D., Gregory, S., Arnason, B. G., & Reder, A. T. (1991). Cytokine levels in the cerebrospinal fluid and serum of patients with multiple sclerosis. *Journal of Neuroimmunology, 32 (1)*, 67-74.

Malek-Ahmadi, P. (1996). Neuropsychiatric aspects of cytokines research: An overview. *Neuroscience and Biobehaviour Review, 20 (3)*, 359-365.

Mantovani, G., Madeddu, C., Gramiganano, G., Ferreli, L., Massa, E., Contu, P., & Serpe, R. (2004). Association of serum IL-6 levels with comprehensive geriatric assessment variables in a population of elderly cancer patients. *Oncology Reports, 11 (1)*, 197-206.

Mapou, R. L., Law, W. A., Martin, A., Kampen, D., Salazar, A. M., & Rundell, J. R. (1993). Neuropsychological performance, mood, and complaints of cognitive and motor difficulties in individuals infected with the human immunodeficiency virus. *Journal of Neuropsychiatry and Clinical Neurosciences, 5*, 86-93.

Marshall, G. D., Agarwal, S. K., Lloyd, C., Cohen, L., Henninger, E. M., & Morris, G. J. (1998). Cytokine dysregulation associated with exam stress in healthy medical students. *Brain, Behavior, and Immunity, 12 (4)*, 297-307.

Martinez-Maza, O. (1992). IL-6 and AIDS. *Research in Immunology, 143 (7)*, 764-769.

Mauri, M., Sinfriani, E., Bono, G., Vignati, F., Berselli, M. E., Attanasio, R., & Nappi, G. (1993). Memory impairments in Cushing's disease. *Acta Neurology Scandanavia, 87*, 52-55.

Mayeux, R., Stern, Y., Tang, M. X., Todak, G., Marder, K., Sano, M., Richards, M., Stein, Z., Ehrhardt, A. A., & Gorman, J. M. (1993). Mortality risks in gay men

with human immunodeficiency virus infection and cognitive impairment. *Neurology, 43 (1)*, 176-182.

McArthur, J. C., Sacktor, O., & Selnes, O. (1999). Human immunodeficiency virus-associated dementia. *Seminars in Neurology, 19 (2)*, 129-150.

McEwen, B. S. (2000). Effects of adverse experiences for brain structure and function. *Biological Psychiatry, 48*, 721-731.

McEwen, B. S., & Stellar, E. (1993). Stress and the individual mechanisms leading to disease. *Archives of Internal Medicine, 153*, 2093-2101.

Mehta, P., Gulevich, S. J., Thal, L. J., Jin, H., Olichney, J. M., McCutchan, J. A., Heaton, R. K., Kirson, D., Kaplanski, G., Nelson, J., Atkinson, J. H., Wallace, M. R., Grant, I., & the HNRC Group. (1996). Neurological symptoms, not signs, are common in early HIV infection. *Journal of Neuro-AIDS, 1*, 67-85.

Mellors, J. W., Munoz, A., Giorgi, J. V., Margolick, J. B., Tassoni, C. J., Gupta, P., Kingsley, L. A., Todd, J. A., Saah, A. J., Detels, R., Phair, J. P., & Rinaldo, C. R. (1997). Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. *Annals of Internal Medicine, 126*, 946-954.

Membreno, L., Irony, I., Dere, W., Klein, R., Biglieri, E. G., & Cobb, E. (1987). Adrenocortical function in acquired immunodeficiency syndrome. *Journal of Clinical Endocrinology and Metabolism, 65 (3)*, 482-487.

Merenich, J. A., McDermott, M. T., Asp, A. A., Harrison, S. M., & Kidd, G. S. (1990). Evidence of endocrine involvement early in the course of human immunodeficiency virus infection. *Journal of Clinical Endocrinology and Metabolism, 70 (3)*, 566-571.

Merrill, J. E., & Chen, I. S. (1991). HIV-1, macrophages, glial cells, and cytokines in AIDS nervous system disease. *FASEB Journal, 5 (10)*, 2391-2397.

Mikova, O., Yakimova, R., Bosmans, E., Kenis, G., & Maes, M. (2001). Increased tumor necrosis factor alpha concentrations in major depression and multiple sclerosis. *European Neuropsychopharmacology, 11*, 203-208.

Millikin, C. P., Rourke, S. B., Halman, M. H., & Power, C. (2003). Fatigue in HIV/AIDS is associated with depression and subjective cognitive complaints but not neuropsychological functioning. *Journal of Clinical and Experimental Neuropsychology, 25 (2)*, 201-215.

Minagar, A., Shapshak, P., Fujimura, R., Ownby, R., Heyes, M., & Eisdorfer, C. (2002). The role of macrophage/microglia and astrocytes in the pathogenesis of three neurologic disorders: HIV-associated dementia, Alzheimer disease, and multiple sclerosis. *Journal of the Neurological Sciences, 202*, 13-23.

Moore, L. H., van Gorp, W. G., Hinkin, C. H., Stern, M. J., Swales, T., & Satz, P. (1997). Subjective complaints versus actual cognitive deficits in predominantly symptomatic HIV-1 seropositive individuals. *Journal of Neuropsychiatry and Clinical Neurosciences, 9*, 37-44.

Mulder, J. W., Frissen, P. H., Krijnen, P., Endert, E., de Wolf, F., Goudsmit, J., Masterson, J. G., & Lange, J. M.(1992). Dehydroepiandrosterone as predictor for progression to AIDS in asymptomatic human immunodeficiency virus-infected men. *Journal of Infectious Diseases, 165*, 413-418.

Muller, N., & Ackenheil, M. (1998). Psychoneuroimmunology and the cytokine action in the CNS: Implications for psychiatric disorders. *Progress in Neuropsychopharmacology and Biological Psychiatry, 22 (1)*, 1-33

Mullington, J. M., Jinze-Selch, D., & Pollmacher, T. (2001). Mediators of inflammation and their interaction with sleep: Relevance for chronic fatigue syndrome and related conditions. *Annals of the New York Academy of Sciences, 933*, 201-210.

Munck, A. Guyre, P. J., & Holbrook, N. J. (1984). Physiological functions of glucocorticoids in stress and their relation to pharmacological actions. *Endocrine Reviews, 5 (1)*, 25-44.

Murr, C., Widner, B., Wirleitner, B., & Fuchs, D. (2002). Neopterin as a marker for immune system activation. *Current Drug Metabolism, 3 (2)*, 175-187.

Musselman, D. L., Miller, A. H., Porter, M. R., Manatunga, A., Gao, F., Penna, S., Pearce, B. D., Landry, J., Glover, S., McDaniel, J. S., & Nemeroff, C. B. (2001). Higher than normal plasma interleukin-6 concentrations in cancer patients with depression: preliminary findings. *American Journal of Psychiatry, 158 (8)*, 1252-1257.

Nair, M. P., Saravolatz, L. D., & Schwartz, S. A.. (1995). Selective inhibitory effects of stress hormones on natural killer (NK) cell activity of lymphocytes from AIDS patients. *Immunological Investigations, 24 (5)*, 689-699.

Natelson, B. H., Denny, T., Zhou, X. D., LaManca, J. J., Ottenweller, J. E., Tiersky, L., DeLuca, J., & Gause, W. C. (1999). Is depression associated with immune activation? *Journal of Affective Disorders, 53*, 179-184.

Newcomer, J. W., Craft, S., Hershey, T., Askins, K., & Bardgett, M. E. (1994). Glucocorticoid-induced impairment in declarative memory performance in adult humans. *Journal of Neuroscience, 14*, 2047-2053.

Newcomer, J. W., Selke, G., Melson, A. K., Hershye, T., Craft, S., Richards, K., & Alderson, A. L. (1999). Decreased memory performance in healthy humans induced by stress-level cortisol treatment. *Archives of General Psychiatry, 56*, 527-533.

Nottet, H. S., Persidsky, Y., Sasseville, V. G., Nukuna, A. N., Bock, P., Zhai, Q. H., Sharer, L. R., Mccomb, R. D., Swindells, S., Soderland, C., & Gendelman, H. E. (1996). Mechanisms of the transendothelial migration of HIV-1 infected monocytes into brain. *Journal of Immunology, 156*, 1284-1295.

Oberfield, S.E., Cowan, L., Levine, L. S., George, A., David, R., Litt, A., Rojas, V., & Kairam, R. (1994). Altered cortisol response and hippocampal atrophy in pediatric HIV disease. *Journal of Acquired Immune Deficiency Syndrome, 7*, 57.

O'Dell, M. W., Meighen, M., & Riggs, R. V. (1996). Correlates of fatigue in HIV infection prior to AIDS: A pilot study. *Disability and Rehabilitation, 18 (5)*, 249-254.

Omdal, R., Mellgren, S. I., Koldingsnes, W., Jacobsen, E. A., & Husby, G. (2002). Fatigue in patients with systemic lupus erythematosus: Lack of associations to serum cytokines, antiphospholipid antibodies, or other disease characteristics. *Journal of Rheumatology, 29 (3)*, 482-486.

Orenstein, J. M. (2001). The macrophage in HIV infection. *Immunobiology, 204 (5)*, 598-602.

Overeem, S., van Vilet, J., Lammers, G. J., Zitman, F. G., Swaab, D. F., & Ferrari, M. D.(2002). The hypothalamus in episodic brain disorders. *The Lancet Neurology, 1*, 437-444.

Pantaleo, G., Graziosi, C., & Fauci, A. S. (1993). New concepts in the immunopathogenesis of human immunodeficiency virus infection. *New England Journal of Medicine, 328 (5)*, 327-335.

Parker, E. S., Eaton, E. M., Whipple, S. C., Heseltine, P. N. R., & Bridge, T. P. (1995). University of Southern California Repeatable Episodic Memory Test. *Journal of Clinical and Experimental Neuropsychology, 17*, 926-936.

Patarca, R., Klimas, N. G., Lugtendorf, S., Antoni, M., & Fletcher, M. A. (1994). Dysregulated expression of tumor necrosis factor in chronic fatigue syndrome: Interrelations with cellular sources and patterns of soluble immune mediator expression. *Clinical and Infectious Diseases, 18 (Suppl 1)*, 147-153.

Patarca, R. (2001). Cytokines and chronic fatigue syndrome. *Annals of New York Academy of Sciences, 933*, 185-200.

Pawlikowski, M., Zelazowski, P., Dohler, K., & Stepien, H. (1988). Effects of two neuropeptides, somatoliberin (GRF) and corticoliberin (CRF) on human lymphocyte natural killer cell activity. *Brain, Behavior, and Immunity, 2 (1)*, 50-56.

Pemberton, L. A., Kerr, S. J., Smythe, G., & Brew, B. J. (1997). Quinolinic acid production by macrophages stimulated with IFN-gamma, TNF-alpha, and IFN-alpha. *Journal of Interferon and Cytokine Research, 17 (10)*, 589-595.

Penninx, B. W., Kritchevsky, S. B., Yaffe, K., Newman, A. B., Simonsick, E. M., Rubin, S., Ferrucci, L., Harris, T., & Pahor, M. (2003). Inflammatory markers and depressed mood in older persons: Results from the Health, Aging and Body Composition study. *Biological Psychiatry, 54 (5)*, 566-572.

Perkins, D. O., Leserman, J., Stern, R. A., Baum, S. F., Liao, D., Golden, R. N., & Evans, D. L. (1995). Somatic symptoms and HIV infection: Relationship to depressive symptoms and indicators of HIV disease. *American Journal of Psychiatry, 152 (12)*, 1776-1781.

Petito, C. K., Roberts, B., Cantando, J. D., Rabinstein, A., & Duncan, R. (2001). Hippocampal injury and alterations in neuronal chemokine co-receptor expression in patients with AIDS. *Journal of Neuropathology and Experimental Neurology, 60*, 377-385.

Poutiainen, E., & Elovaara, I. (1996). Subjective complaints of cognitive symptoms are related to psychometric findings of memory deficits in patients with HIV-1 infection. *Journal of the International Neuropsychological Society, 2*, 219-225.

Poutiainen, E., Elovaara, I., Raininko, R., Hokkanen, L., Valle, S. L., Lahdevirta, J., & Iivanainen, M. (1993). Cognitive performance in HIV-1 infection: Relationship to severity of disease and brain atrophy. *Acta Neurologica Scandinavica, 87*, 88-94.

Rabkin, J. G., McElhiney, M., Ferrando, S. J., Van Gorp, W., & Lin, S. H. (2004). Predictors of employment of men with HIV/AIDS: A longitudinal study. *Psychosomatic Medicine, 66 (1)*, 72-78.

Raininko, R., Elovaara, I., Virta, A., Valanne, L., Haltia, M., & Valle, S. L (1992). Radiological study of the brain at various stages of human immunodeficiency

virus infection: Early development of brain atrophy. *Neuroradiology, 34*, 190-196.

Rasmuson, S., Andrew, R., Nasman, B., Seckl, J. R., Walker, B. R., & Olsson, T. (2001). Increased glucocorticoid production and altered cortisol metabolism in women with mild to moderate Alzheimer's disease. *Biological Psychiatry, 49*, 547-552.

Reed, G. M., Kemeny, M. E., Taylor, S. E., & Visscher, B. R. (1999). Negative HIV-specific expectancies and AIDS-related bereavement as predictors of symptom onset in asymptomatic HIV-positive gay men. *Health Psychology, 18*, 354-363.

Reichenberg, A., Yirmiya, R., Schuld, A., Kraus, T., Haack, M., Morag, A., & Pollmaecher, T. (2001). Cytokine-associated emotional and cognitive disturbances in humans. *Archives of General Psychiatry, 58 (5)*, 445-452.

Reitan, R. M., & Wolfson, D. (1993). *The Halstead-Reitan Neuropsychological Test Battery: Theory and Clinical Interpretation.* (2nd ed.). Tucson, AZ: Neuropsychology Press.

Rentzos, M., Nikolaou, C., Rombos, A., Voumvourakis, K., Segditsa, I., & Papageorgiou, C. (1996). Tumor necrosis factor alpha is elevated in serum and cerebrospinal fluid in multiple sclerosis and inflammatory neuropathies. *Journal of Neurology, 243 (2)*, 165-170.

Resnick, L., Berger, J. R., Shapshak, P., & Tourtellotte, W. W. (1988). Early penetration of the blood-brain barrier by HIV. *Neurology, 38*, 9-14.

Ressler, K. J., & Nemeroff, C. B., (2000). Role of serotonergic and noradrenergic systems in the pathophysiology of depression and anxiety disorders. *Depression and Anxiety, 12*, 2-19.

Reyes, E., Mohar, A., Mallory, M., Miller, A., & Masliah, E. (1994). Hippocampal involvement associated with human immunodeficiency virus encephalitis in Mexico. *Archives of Pathology and Laboratory Medicine, 118 (11)*, 1130-1134.

Robertson, K., Fiscus, S., Kapoor, C., Robertson, W., Schneider, G., Shepard, R., Howe, L., Silva, S., & Hall, C. (1998). CSF, plasma viral load and HIV associated dementia. *Journal of Neurovirology, 4*, 90-94.

Rook, G. A., Onyebujon, P., & Stanford, J. L. (1993). Th1/Th2 switching and loss of CD4 T cells: An immunoendocrinological hypothesis not exclusive to HIV. *Immunology Today, 14 (11)*, 568-569.

Rothwell, N. J., & Luheshi, G. (1994). Pharmacology of interleukin-1 actions in the brain. *Advances in Pharmacology, 25*, 1-20.

Rourke, S. B., Halman, M. H., & Bassel, C. (1999a). Neurocognitive complaints in HIV-infection and their relationship to depressive symptoms and neuropsychological functioning. *Journal of Clinical and Experimental Neuropsychology, 21 (6)*, 737-756.

Rourke, S. B., Halman, M. H., & Bassel, C. (1999b). Neuropsychiatric correlates of memory-metamemory dissociations in HIV-infections. *Journal of Clinical and Experimental Neuropsychology, 21 (6)*, 757-768.

Roux-Lombard, P., Modoux, C., Cruchaud, C., & Dayer, J. M (1989). Purified blood monocytes from HIV-1 infected patients produce high levels of TNF-alpha and IL-1. *Clinical Immunology and Immunopathology, 50*, 374-384.

Royal, W., Selnes, O. A., Concha, M., Nance-Sproson, T. E., & McArthur, J. C. (1994). Cerebrospinal fluid HIV-1 p24 antigen levels in HIV-1 related dementia. *Annals of Neurology, 36*, 32-39.

Ruff, R. M., & Allen, C. C. (1999). *Ruff-Light Trail Learning Test.* Odessa, FL: Psychological Assessment Resources, Inc.

Ryan, L. A., Zheng, J., Brester, M., Bohac, D., Hahn, F., Anderson, J., Ratanasuwan, W., Gendelman, H. E., & Swindells, S. (2001). Plasma level of soluble CD14 and tumor necrosis factor-alpha type II receptor correlate with cognitive dysfunction during human immunodeficiency virus type 1 infection. *Journal of Infectious Diseases, 15, 184 (6)*, 699-706.

Sacktor, N. C., Bacellar, H., Hoover, D. R., Nance-Sproson, T. E., Selnes, O. A., Miller, E. N., DalPan, G. J., Kleeberger, C., Brown, A., Saah, A., & McArthur, J. C. (1996). Psychomotor slowing in HIV infection: A predictor of dementia, AIDS and death. *Journal of Neurovirology, 2 (6)*, 404-410.

Salvaggio, A., Balotta, C., Galli, M., & Clerici, M. (1995). CD4 count in HIV infection is positively correlated to interferon-gamma and negatively correlated to interleukin-10 in vitro production. *AIDS, 10*, 449-451.

Sapolsky, R., Rivier, C., Yamamoto, G., Plosky, P., & Vale, W. W. (1987). Interleukin-1 stimulates the secretion of hypothalamic corticotropin-releasing factor. *Science, 238*, 522-524.

Sapse, A. T. (1997). Cortisol, high cortisol diseases and anti-cortisol therapy. *Psychoneuroendocrinology, 22 (Suppl. 1)*, 3-10.

Schifitto, G., McDermott, M. P., Evans, T., Fitzgerald, T., Schwimmer, J., Demeter, L., & Kieburtz. (2000). Autonomic performance and dehydroepiandrosterone sulphate levels in HIV-1-infected individuals: Relationship to TH1 and TH2 cytokine profile. *Archives of Neurology, 57 (7)*, 1027-1032.

Schlatter, J., Ortuno, F., & Cervera-Enguiz, S. (2004). Monocytic parameters in patients with dysthymia versus major depression. *Journal of Affective Disorders, 78*, 243-247.

Seilehan, D., Kobayashi, K., He, Y., Uchilhara, T., Rosenblum, O., Katlama, C., Bricaire, F., Duyckaerts, C., & Hauw, J. J. (1997). Tumor necrosis factor-alpha, microglia and astrocytes in AIDS dementia complex. *Acta Neuropathologica (Berlin), 93 (5)*, 508-517.

Sendi, P. P., Bucher, H. C., Craig, B. S., Pfluger, D., & Battegay, M. (1999). Estimating AIDS-free survival in a severely immunosuppressed asymptomatic HIV-infected population in the era of antiretroviral triple combination therapy. *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology, 20 (4)*, 376-381.

Sheline, Y. I., Wang, P. W., Gado, M. H., Csernansky, J. C., & Vannier, M. W. (1996). Hippocampal atrophy in recurrent major depression. *Proceedings of the National Academy of Science of the USA, 93 (9)*, 3908-3913.

Singer, E. J., Syndulko, K., Fahy-Chandon, B. N. , Shapshak, P., Resnick, L., Schmid, P., Conrad, A. J., & Tourtellotte, W. W. (1994). Cerebrospinal fluid p24 antigen levels and intrathecal immunoglobulin G synthesis are associated with cognitive disease severity in HIV-1. *AIDS, 8*, 197-204.

Sluzewska, A., Rybakowski, J., Bosmans, E., Sobieska, M., Berghmans, R., Maes, M., & Wiktorowicz, K. (1996). Indicators of immune activation in major depression. *Psychiatry Research, 64*, 161-167.

Sluzewska, A., Rybakowski, J. K., Laciak, M., Mackiewicz, A., Sobieska, M., & Wiktorowicz, K. (1995). Interleukin-6 serum levels in depressed patients before and after treatment with fluoxetine. *Annals of New York Academy of Sciences, 762*, 474-476.

Spath-Schwalbe, E., Hansen, K., Schmidt, F., Schrezenmeier, H., Marshall, L., Burger, K., Fehm, H. L., & Born, J. (1998). Acute effects of recombinant human interleukin-6 on endocrine and central nervous sleep functions in health men. *Journal of Clinical Endocrinology and Metabolism, 83 (5)*, 1573-1579.

Spreen, O., & Strauss, E. (1991). *A compendium of neuropsychological tests: Administration, norms, and commentary*. New York: Oxford University Press.

Smith, E. M., & Blalock, J. E. (1982). Human lymphocyte production of ACTH and endorphin-like substances: Association with leukocyte interferon. *Proceedings of the National Academy of Science of the USA, 78*, 7530-7534.

Solomon, G. F., Ironson, G. H., & Balbin, E. G. (2000). Psychoneuroimmunology of HIV/AIDS. *Annals New York Academy of Sciences, 917*, 500-504.

Sorensen, P. S. (1999). Biological markers in body fluids for activity and progression in multiple sclerosis. *Multiple Sclerosis, 5 (4)*, 287-290.

Song, C., & Leonard, B. E. (1994). An acute phase protein response in the olfactory bulbectomised rat: Effect of sertraline treatment. *Medical Sciences Research, 22*, 313-314.

Squire, L. R. (1992). Memory and the hippocampus: A synthesis from findings with rats, monkeys and humans. *Psychological Review, 99 (2)*, 195-231.

Squire, L. R., Knowlton, B., & Musen, G. (1993). The structure and organization of memory. *Annual Review of Psychology, 44*, 453-495.

Squire, L. R., Stark, C. E. L., & Clark, R. E. (2004). The medial temporal lobe. *Annual Reviews in Neuroscience, 27*, 279-306.

Starkman, M. N., Gebarski, S. S., Berent, S., & Schteingart, D. E. (1992). Hippocampal formation volume, memory dysfunction, and cortisol levels in patients with Cushing's syndrome. *Biological Psychiatry, 32*, 756-765.

Staszewski, S., DeMasi, R., Hill, A. M., & Dawson, D. (1998). HIV-1 RNA, CD4 cell count and the risk of progression to AIDS and death during treatment with HIV-1 reverse transcriptase inhibitors. *AIDS, 12 (15)*, 1991-1997.

Stordal, K. I., Lundervold, A. J., Egeland, J., Mykletun, A., Asbjornsen, A., Landro, N. I., Roness, A., Rund, B. R., Sundet, K., & Oedegaard, K. J., & Lund, A. (2004). Impairment across executive functions in recurrent major depression. Nordic *Journal of Psychiatry, 58 (1)*, 41-47.

Stylianou, E., Aukrust, P., Bendtzen, K., Muller, F., & Froland, S. S. (2000). Interferons and interferon (IFN)-inducible protein 10 during highly active anti-retroviral therapy (HAART)-possible immunosuppressive role of IFN-alpha in HIV infection. *Clinical and Experimental Immunology, 119 (3)*, 479-485.

Suarez, E. C., Krishnan, R. R., & Lewis, J. G. (2003). The relation of severity of depressive symptoms to monocyte-associated proinflammatory cytokines and chemokines in apparently healthy men. *Psychosomatic Medicine, 65*, 362-368.

Swain, M. G. (2000). Fatigue in chronic disease. *Clinical Science, 99 (1)*, 1-8.

Tekin, S., & Cummings, J. L. (2002). Frontal-subcortical neuronal circuits and clinical neuropsychiatry: An update. *Journal of Psychosomatic Research, 53*, 647-654.

Tozzi, V., Balestra, P., Murri, R., Galgani, S., Bellagamba, R., Narciso, P., Antinori, A., Giulianelli, M., Tosi, G., Fantoni, M., Sampaolesi, A., Noto, P., Ippolito, G., & Wu, A. W. (2004). Neurocognitive impairment influences quality of life in HIV-infected patients receiving HAART. *International Journal of Sexually Transmitted Diseased & AIDS, 15 (4)*, 254-259.

Trzonkowski, P., Myliwska, J., Godlewska, B., Szmit, E., Ukaszuk, K., Wickiewicz, J., Brydak, L., Machaa, M., Landowski, J., & Myliwski, A. (2004). Immune consequences of the spontaneous pro-inflammatory status in depressed elderly patients. *Brain, Behaviour, and Immunity, 18 (2)*, 135-148.

Tulving, E., & Markowitsch, H. J. (1998). Episodic and declarative memory: Role of the hippocampus. *Hippocampus, 8 (3)*, 198-204.

Tyor, W. R., Glass, J. D., Griffin, J. W., Becker, P. S., McArthur, J. C., Bezman, L., & Griffin, D. E. (1992). Cytokine expression in the brain during the acquired immunodeficiency syndrome. *Annals of Neurology, 31 (4)*, 349-360.

Umegaki, H., Ikari, H., Nakahata, H., Endo, H., Suzuki, Y., Ogawa, O., Nakamura, A., Yamamot, T., & Iguchi, A. (2000). Plasma cortisol levels in elderly female subjects with Alzheimer's disease: A cross-sectional and longitudinal study. *Brain Research, 881*, 241-243.

Vacca, A., Felli, M. P., Farina, A. R., Martinotti, S., Maroder, M., Screpanti, I., Meco, D., Petrangeli, E., Frati, L., & Gulino, A. (1992). Glucocorticoid receptor mediated

suppression of the interleukin-2 gene expression through impairment of the cooperativity between nuclear factors of activated T cells and AP 1 enhancer elements. *Journal of Experimental Medicine, 175 (3)*, 637-646.

Valdez, H., & Lederman, M. M. (1997-1998). Cytokines and cytokine therapies in HIV infection. *AIDS Clinical Review*, 187-228.

van Gorp, W. G., Satz, P., Hinkin, C., Selnes, O., Miller, E. N., McArthur, J., Cohen, B., & Paz, D. (1991). Metacognition in HIV-1 seropositive asymptomatic individuals: Self-ratings versus objective neuropsychological performance. Multicenter AIDS Cohort Study (MACS). *Journal of Clinical and Experimental Neuropsychology, 13*, 812-819.

Vago, L., Trabattoni, G., Lechi, A., Cristina, S., & Budka, H. (1990). Neuropathology of AIDS dementia: A review after 205 post mortem examinations. III national meeting: AIDS and correlated syndromes. *Acta Neurologica, 12*, 32-35.

van Gorp, W. G., Mandelker, M. A., Gee, M., Hinkin, C. H., Stern, C. E., Paz, D. K., Dixon, W., Evans, G., Flynn, F., Frederick, C. J., Ropchan, J. R., & Blahd, W. H. (1992). Cerebral metabolic dysfunction in AIDS: Findings in a sample with and without dementia. *The Journal of Neuropsychiatry and Clinical Neurosciences, 4*, 280-287.

Van Londen, L., Goekoop, J. G., Zwinderman, A. H., Lanser, J. B. K., Wiegant, V. M., & De Wied, D. (1998). Neuropsychological performance and plasma cortisol, arginine vasopressin and oxytocin in patients with major depression. *Psychological Medicine, 28 (2)*, 275-284.

Vedhara, K., Hyde, J., Gilchrist, I. D., Tytherleigh, M., & Plummer, S. (2000). Acute stress, memory, attention and cortisol. *Psychoneuroendocrinology, 25 (6)*, 535-549.

Veiel, H. O. F. (1997). A preliminary profile of neuropsychological deficits associated with major depression. *Journal of Clinical and Experimental Neuropsychology, 19*, 587-603.

Villette, J. M, Bourin, P., Doinel, C., Mansour, I., Fiet, J., Boudou, P., Dreux, C., Roue, R., Debord, M., & Levi, F. (1990). Circadian variations in plasma levels of hypophyseal, adrenocortical and testicular hormones in men infected with human immunodeficiency virus. *Journal of Clinical Endocrinology and Metabolism, 70 (3)*, 572-577.

Vgontzas, A. N., Papanicolaou, D. A., Bixler, E. O., Lotsikas, A., Zachman, K., Kales, A., Prolo, P., Wong, M., Licinio, J., Gold, P. W., Hermida, R. C., Mastorakos, G., & Chrousos, G. P. (1999). Circadian Interleukin-6 secretion and quantity and depth of sleep. *The Journal of Clinical Endocrinology & Metabolism, 84 (8)*, 2603-2607.

Vgontzas, A. N., Papanicolaou, D. A., Bixler, E. O., Hopper, K., Lotsikas, A., Lin, H. M., Kales, A., & Chrousos, G. P. (2000). Sleep apnea and daytime sleepiness and fatigue: Relation to visceral obesity, insulin resistance, and hypercytokinemia. *Journal of Clinical Endocrinology and Metabolism, 85 (3)*, 1151-1158.

Vyakarnam, A., McKeating, J., Meager, A., & Beverley, P. C. (1990). Tumor necrosis factors (alpha, beta) induced by HIV-1 in peripheral blood mononuclear cells potentiate virus replication. *AIDS, 4 (1)*, 21-27.

Wallace, D. J., Linker-Israeli, M., Hallegua, D., Silverman, S., Silver, D., & Weisman, M. H. (2001). Cytokines plan an aetiopathogenetic role in fibromyalgia: A hypothesis and pilot study. *Rheumatology, 40*, 743-749.

Wang, J., Asensio, V. C., & Campbell, I. L. (2002). Cytokines and chemokines as mediators of protection and injury in the central nervous system assessed in transgenic mice. *Current Topics in Microbiology and Immunology, 265*, 23-48.

Watkins, L. R., Maier, S. F., & Goehler, L. E. (1995). Cytokine-to-brain communication: A review and analysis of alternative mechanisms. *Life Sciences, 57*, 1011-1026.

Weaver, J. D., Huang, M. H., Albert, M., Harris, T., Rowe, J. W., & Seeman, T. E. (2002). Interleukin-6 and risk of cognitive decline: MacArthur studies of successful aging. *Neurology, 59 (3)*, 371-378.

Weber, J. (2001). The pathogenesis of HIV-1 infection. *British Medical Bulletin, 58*, 61-72.

Wechsler, D. (1997). *Wechsler Memory Scale - Third Edition Administration andScoring Manual.* San Antonio, TX: The Psychological Corporation.

Weiner, M. F., Vobach, S., Olsson, K., Svetlik, D., & Risser, R. C. (1997). Cortisol secretion and Alzheimer's disease progression. *Biological Psychiatry, 42 (11)*, 1030-1038.

Weizman, R., Laor, N., Podliszewski, E., Notti, I., Djaldetti, M., & Bessler, H. (1994). Cytokine production in major depressed patients before and after clomipramine treatment. *Biological Psychiatry, 35*, 42-47.

Wesselingh, S. L., Glass, J., McArthur, J. C., Griffin, J. W., & Griffin, D. E. (1994). Cytokine dysregulation in HIV-associated neurological disease. *Advances in Neuroimmunology, 4*, 199-206.

Wesselingh, S. L., Power, C., Glass, J. D., Tyor, W. R., McArthur, J. C., Farber, J. M., Griffin, J. W., & Griffin, D. E. (1993). Intracerebral cytokine messenger RNA expression in acquired immunodeficiency syndrome dementia. *Annals of Neurology, 33 (6)*, 576-582.

White, D. A., Heaton, R. K., Monsch, A. U., & the HNRC Group. (1995). Neuropsychological studies of asymptomatic Human Immunodeficiency Virus Type 1 infected individuals. *Journal of the International Neuropsychological Society, 1*, 304-315.

Widner, B., Laich, A., Sperner-Unterweger, B., Ledochowski, M., & Fuchs, D. (2002). Neopterin production, tryptophan degradation, and mental depression—what is the link? *Brain and Behavioural Immunology, 16 (5)*, 590-595.

Widner, B., Leblhuber, F., Walli, J., Tilz, G. P., Demel, U., & Fuchs, D. (2000). Tryptophan degradation and immune activation in Alzheimer's disease. *Journal of Neural Transmission, 107*, 343-353.

Widner, B., Sepp, N., Kowald, E., Kind, S., Schmuth, M., & Fuchs, D. (1999). Degradation of tryptophan in patients with systemic lupus erythematosus. *Advances in Experimental Medicine and Biology, 467*, 571-577.

Wiley, C. A., Masliah, E., Morey, M., Lemere, C., DeTeresa, R., Grafe, M., Hansen, L., & Terry, R. (1991). Neocortical damage during HIV infection. *Annals of Neurology, 29*, 651-657.

Williams, R. A., Hagerty, B. M., Cimprich, B., Therrien, B., Bay, E., Oe, H., (2000). Changes in directed attention and short-term memory in depression. *Journal of Psychiatric Research, 34,* 227-238.

Wilkie, F. L., Goodkin, K., Eisdorfer, C., Feaster, D., Morgan, R., Fletcher, M. A., Blaney, N., Baum, M., & Szapocznik, J. (1998). Mild cognitive impairment and risk of mortality in HIV-1 infection. *Journal of Neuropsychiatry and Clinical Neurosciences, 10*, 125-132.

Wilkins, J. W., Robertson, K. R., Snyder, C. R., Robertson, W. K., van der Horst, C., & Hall, C. D. (1991). Implications of self-reported cognitive and motor dysfunction in HIV-positive patients. *American Journal of Psychiatry, 148*, 641-643.

Wiseman, M. B., Sanchez, J. A., Buechel, C., Mintun, M. A., Lopez, O. L., Milko, D., & Becker, J. T. (1999). Patterns of relative cerebral blood flow in minor cognitive motor disorder in human immunodeficiency virus infection. *Journal of Neuropsychiatry and Clinical Neurosciences, 11 (2)*, 222-233.

Wolf, O. T., Schommer, N. C., Hellhammer, D. H., McEwen, B. S., & Kirchbaum, C. (2001). The relationship between stress induced cortisol levels and memory differs between men and women. *Psychoneuroendocrinology, 26 (7)*, 711-720.

Wolkowitz, O. M., Reus, V. I., Weingartner, H., Thompson, K., Breier, A., Dorna, A., Rubinow, D., & Pickar, D. (1990). Cognitive effects of corticosteroids. *American Journal of Psychiatry, 147 (10)*, 1297-1303.

Woloski, B. M., Smith, E. M., Meyer, W. J., Fuller, G. M., & Blalock, J. E. (1985). Corticotrophin-releasing activity of monokines. *Science, 230 (4729)*, 1035-1037.

Wratten, C., Kilmurray, J., Nash, S., Seldon, M., Hamilton, C. S., O'Brien, P. C., & Denham, J. W. (2004). Fatigue during breast radiotherapy and its relationship to biological factors. *International Journal of Radiation Oncology, Biology, Physics, 59 (1)*, 160-167.

Wright, S. C., Jewett, A., Mitsuyasu, R., & Bonavida, B. (1988). Spontaneous cytotoxicity and tumor necrosis factor production by peripheral blood monocytes from AIDS patients. *Journal of Immunology, 141 (1)*, 99-104.

Xia, Z., DePierre, J. W., & Nassberger, L. (1996). Tricyclic antidepressants inhibit IL-6, IL-1beta and TNF-alpha release in human blood monocytes and IL-2 and Interferon-gamma in T cells. *Immunopharmacology, 34*, 27-37.

Yaffe, K., Lindquist, K., Penninx, B. W., Simonsick, E. M., Pahor, M., Kritchevsky, S., Launer, L., Kuller, L., Rubin, S., & Harris, T. (2003). Inflammatory markers and cognition in well-functioning African-American and white elders. *Neurology, 61*, 76-80.

Zangerle, R., Widner, B., Quirchmair, G., Neurauter, G., Sarcletti, M., & Fuchs, D. (2002). Effective antiretroviral therapy reduces degradation of tryptophan in patients with HIV-1 infection. *Clinical Immunology, 104 (3)*, 242.

Zautra, A. J., Burleson, M. H., Matt, K. S., Roth, S., & Burrows, L. (1994). Interpersonal stress, depression, and disease activity in rheumatoid arthritis and osteoarthritis patients. *Health Psychology, 13 (2)*, 139-148.

Zautra, A. J., Yocum D. C., Villanueva, I., Smith, B., Davis, M. C., Attrep, J., & Irwin, M. (2004). Immune activation and depression in woman with rheumatoid arthritis. *Journal of Rheumatology, 31 (3)*, 457-463.

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